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PROCEEDINGS
of the
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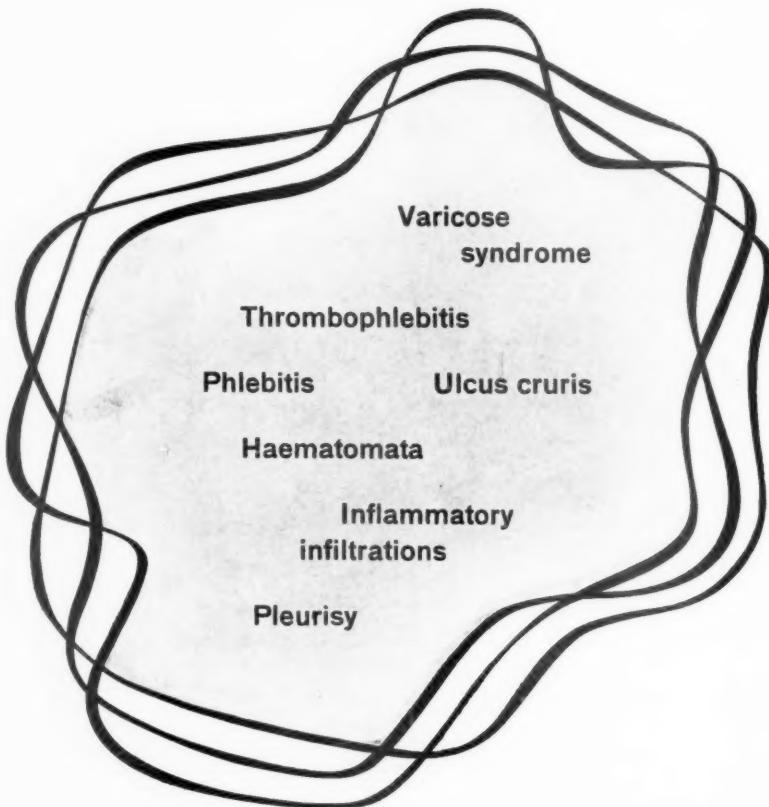
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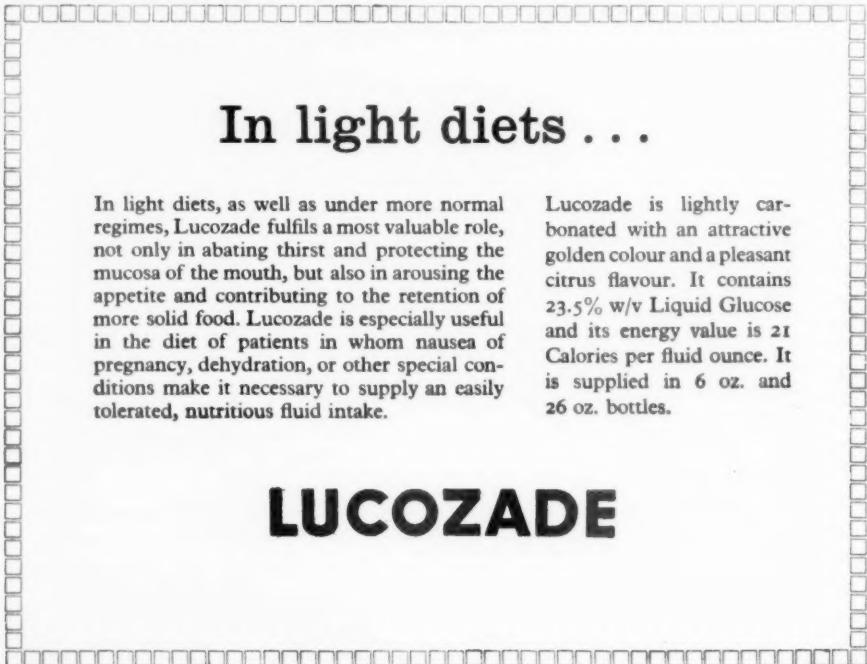
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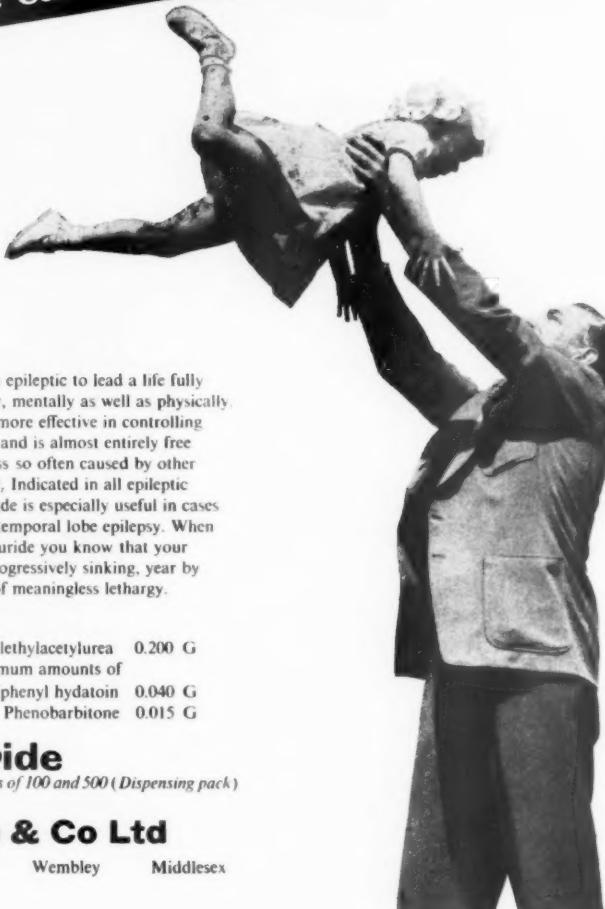
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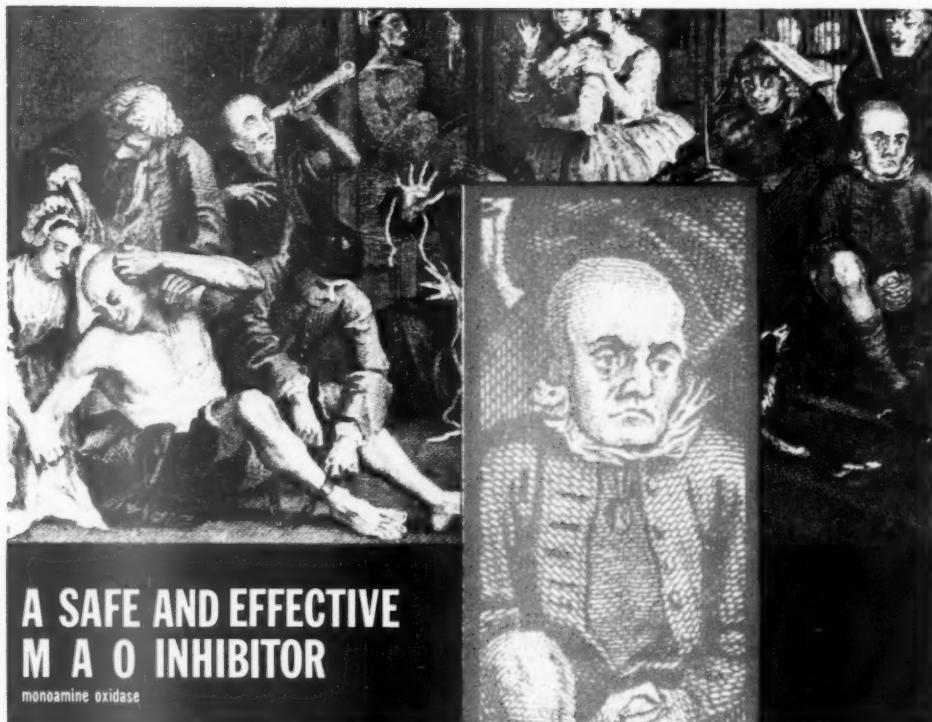
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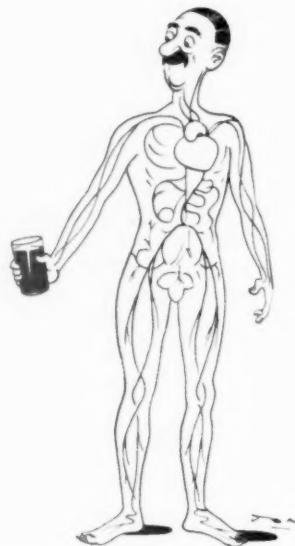
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Meeting
November 20, 1959

Radiology in Surgery of the "Acute Abdomen" [Abridged]

By H. DENDY MOORE, M.C., F.R.C.S., F.R.C.S.Ed.

Exeter

(1) In Avoiding Surgery for Medical Conditions

Many patients, especially children, are referred to a surgeon with abdominal pain from pneumonia, spinal disease and other medical conditions in whom the diagnosis is in such doubt that, without radiology, laparotomy would be performed. For example, abdominal pain in a boy of 19 months could not be explained until X-rays (Fig. 1) showed the regular density of the diaphyses of the long bones, due to the deposition of lead phosphate, which occurs in lead poisoning in children.



FIG. 1.—X-ray films of a child of 1 year 7 months complaining of abdominal pain, showing the regular density of the diaphyses of the long bones due to deposition of lead phosphate which occurs in lead poisoning in children. (Courtesy of Dr. F. Brimblecombe.)

It is easy, however, to make the opposite error and be led astray by the radiological findings. A plain X-ray picture of the abdomen may show fluid levels in the gut, not due to intestinal obstruction but to a previous enema, to intestinal hurry or to ileus. Alternatively, obstruction may be present without fluid levels, especially if the block is incomplete. Obstructed gut in the chest is often mistaken for a pleural effusion (Moore, 1950). When the intestine in the thorax is strangulated, the position is even more difficult because there will be a serosanguineous effusion, which may be large, and if the stomach only is strangulated the sole abdominal symptom will be vomiting and there will be no abdominal signs clinical or radiological.

(2) To Confirm or Establish a Diagnosis

Where a diagnosis is in doubt, radiology may clarify the position; this was discussed in cases of trauma, perforated peptic ulcer, inflammation and obstruction. For example, X-ray pictures of the chest of a man with thoracic injury showed a pneumothorax and localized fluid levels, indicating gut in the chest through a ruptured diaphragm. Free gas below the diaphragm indicated gross error in the diagnosis made in various patients with acute abdominal pain. The diagnosis of acute cholecystitis where there is pain in the right hypochondrium, fever, localized tenderness and a lump in the region of the gall bladder, may be supported by showing gall stones by X-ray—but X-ray pictures in such patients may alter the diagnosis, which is demonstrated by Fig. 2, where a subphrenic abscess is shown. A similar story, followed by signs of intestinal obstruction, with a film showing gas in the biliary tree and an opaque gall stone in the ileum, makes the diagnosis of gall-stone ileus simple; more often, however, the clinical side is obscure and radiology less helpful. Intestinal obstruction may be in some doubt; films were shown of intussusceptions, in a child and an adult, where the diagnosis was made by barium enemas.

(3) To Decide on the Correct Treatment in an "Acute Abdomen"

Most of the patients considered in (2) would

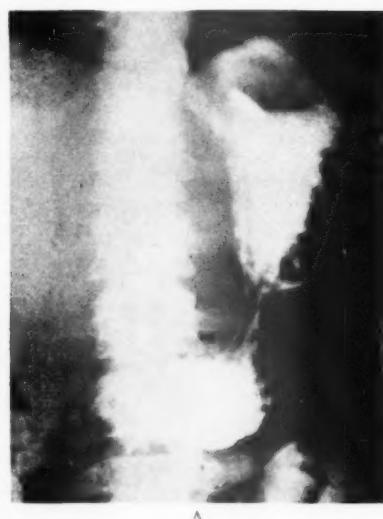


FIG. 2.—X-ray film of a woman of 48, who had pain in the right hypochondrium, fever and a tender mass, diagnosed as acute cholecystitis, showing a subphrenic abscess.

probably have been operated upon with a diagnosis of "acute abdomen, laparotomy necessary" without the help of the X-ray findings: but when a correct diagnosis has been made, it is better to begin an operation knowing the site of the lesion—which is exemplified in intestinal obstruction, where the site of the obstruction can often be demonstrated by plain X-ray films.

In babies with *imperforate anus*, the operation done when the gut is close to the anal dimple differs vastly from that necessary when there is wide separation. It has been stated (Wangensteen and Rice, 1930; Paine and Nessa, 1942) that gas will descend in the gut of these babies to the lower limit of the colon and that the distance from anal dimple to colon can be judged radiologically. This, however, is not always so as in a case shown where the gut reached the prostate, although gas in the gut was well above the pelvic brim.

There is good evidence (Moore, 1955) that *perforated gastric ulcers* are best treated by partial gastrectomy. A method of diagnosing these on admission to hospital would, therefore, be of great value and it is suggested that this can be done in the following way. Instead of taking the usual plain films of the abdomen, 30 ml of viscous diodone and 30 ml of water, or 40 ml of 35% diodone are instilled into the stomach. Two films are then taken erect with a ten-minute interval, and a third supine. Slides were shown of the results in the normal and in cases of proved duodenal and gastric perforations and Fig. 3 shows the findings with a gastric ulcer. The method appears to be safe as only very little of the diodone escapes into the peritoneal cavity and, even if it does, it seems to be harmless, as it is used in salpingography in large quantities without apparent ill-effects (Kjellberg, 1942; Jefferiss and Samuel, 1946; Bergin, 1951). 57 patients have been examined in this way.



A



B

FIG. 3.—Prepyloric perforations. Erect, A, and supine, B, films of a patient with a prepyloric perforation in whom 30 ml of viscous diodone and 30 ml of water had been put into the stomach. The erect film shows no escape of diodone, but the supine, taken seven minutes later, shows escape. Diodone has not passed into the duodenum.

obtaining a good outline of the stomach in each. There were 3 gastric ulcers in 38 perforations—I was a pinpoint hole which was not demonstrated pre-operatively; the other 2 were well seen (Fig. 3). Of the 35 duodenal ulcers only 6 showed escape of diodone through the perforation, but in none was a misdiagnosis made.

While the series is small, it does suggest that a gastric ulcer can be shown in this way.

Patients with *ulcerative colitis* who are being treated with cortisone sometimes have distension of the abdomen which is shown by X-ray to be due to gross dilatation of the colon. These patients are in need of immediate colectomy to forestall perforation.

(4) *Radiology in the Treatment of the "Acute Abdomen"*

Intussusception in babies can be reduced completely and permanently by means of enemas under radiological control and, even if not completely reduced, the partial reduction can simplify the operation. Slides were shown to illustrate failure, partial reduction and complete reduction and three points were raised if the method is to be used: (1) A radiologist who is convinced that it can be done should be chosen. (2) The child must be properly sedated. (3) A surgeon must be called before reduction is attempted and the theatre prepared for operation in case the attempt fails.

In patients with *volvulus of the sigmoid colon* emergency operation can often be avoided by

passing a tube, through a sigmoidoscope, beyond the twist, thereby relieving the obstruction and allowing the bowel to be prepared for a one-stage operation.

(5) *The Unexpected*

The unexpected occurs from time to time. For example, unexplained peritonitis in lunatics may be due to needles or other sharp objects. A slide was shown of a woman of 70 with an abdominal tumour due to a retractor left in the abdomen thirty years before.

In conclusion, although radiology in the "acute abdomen" can be misleading and may not be of help, it is much more often of great value and often indispensable.

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The Use of Contrast Medium in the Investigation of the Acute Abdomen

By ERIC SAMUEL

Edinburgh

THE material presented results from the use of contrast medium in the diagnosis of obscure acute abdominal catastrophes admitted to the wards of the Royal Infirmary of Edinburgh during 1959. The figures represent only a fraction of the admissions of acute abdominal conditions, being confined to those deemed suitable for investigation by this technique.

To date, one of the main disadvantages of using contrast medium in the diagnosis of acute abdominal conditions has been the lack of a suitable material. Few people feel justified in loading the bowel of a gravely ill patient with barium sulphate in an attempt to determine the nature of some acute abdominal lesion. Furthermore, should the patient be submitted to surgical operation, the post-operative period is undoubtedly far more uncomfortable when the colon is loaded with inspissated barium sulphate.

The advent, however, of the triiodo compounds enabled a water-soluble contrast medium to be made which was fluid and yet possessed sufficient contrast for acute gastro-intestinal lesions to be investigated. The material was made tolerably palatable by the addition of flavouring. The preparation that we have used is: 76% Urografin combined with a non-ionic wetting agent,

flavouring agent and saccharine. This is almost identical to Gastrograffin. It is somewhat bitter but is not unpalatable if diluted with water.

We prepare 100 c.c. of the solution and use 30-40 c.c. for each examination of the upper gastro-intestinal tract, depending on the size of the patient. If the solution is administered by mouth the medium is diluted with 10-15 c.c. of water. If, however, it is administered through an intestinal tube, it is undiluted. The solution is made up in relatively small quantities so that a fresh solution is usually available; it should be stored away from sunlight in a dark container.

Oral contrast medium has been used primarily for the investigation of haemorrhages from the upper gastro-intestinal tract, leaks and perforations from the alimentary canal and also in the identification of the nature and site of intestinal obstruction.

In addition to the use of the oral water-soluble contrast medium for the investigation of gastro-intestinal lesions, contrast medium has been used for intravenous cholangiography and intravenous urography.

Hæmatemesis and Melæna

Until recently it has largely been the practice



FIG. 1.



FIG. 2.



FIG. 3.

FIG. 1-3.—Demonstrating the portions of the alimentary canal filled in the different positions. The first position, the left supine oblique, demonstrates the lower end of the oesophagus and fundus of the stomach. The second position with the patient in the semi-right oblique position demonstrates the body of the stomach, the third right lateral position demonstrates the duodenal cap.

to perform an X-ray examination in a case of haematemesis or severe melena only after a period of conservative treatment. This caused undue stay in hospital and delay in diagnosis. Furthermore, the acute causes of haemorrhage may have completely disappeared by the time the radiological examination has been performed. By the use of water-soluble medium and meticulous attention to a "no-touch" technique, it has been possible to examine patients with haematemesis and melena immediately on admission. Provided that the clinical condition is controlled and that anti-shock and resuscitative measures have been successful, the patient is submitted to an X-ray examination as soon as the clinical condition warrants it.

The "no-touch" technique consists of using the supine position, avoiding palpation of the abdomen. The use of the supine position has been sufficient to outline the mucosal pattern of the stomach and the duodenum. In this series of 100 cases, 33 patients with haematemesis and melena were examined (Table I). Recently

disturbance than the lifting of a patient in bed and the changing of films when a portable bedside unit is used. The results more than justify the transfer of the patient, with adequate precautions, to the X-ray department and performance of a "no-touch" technique on a set capable of delivering high outputs compatible with normal techniques.

The technique of examination is important and Figs. 1, 2 and 3 illustrate the basic principles of the method. While using gravity and posture to keep the bolus of the contrast medium intact, relatively good filling of the various portions of the stomach can be obtained and an adequate mucosal relief study by utilizing the air bubble in the stomach to obtain a double contrast effect. Filming is performed in the various positions and it is important that the fluoroscopic examination be mainly limited to controlling the films to be obtained.

The illustrations of the various types of lesions shown in Figs. 4 and 5 show that the density of the medium is surprisingly good and indeed it has numerous advantages over the use of barium in the diagnosis of acute lesions of the gastro-intestinal tract. Such is the miscibility of the medium with intestinal contents that cavities and ulcers fill considerably more readily than with barium sulphate. One of the interesting findings in the radiological appearances of duodenal ulceration has been the comparative absence of spasm within the duodenal cap. The ulcer is demonstrated as a double density when viewed "en face", frequently surrounded by a "halo" representing an area of oedema. Demonstration of the ulcer in profile is seldom achieved. Gastric ulcers are more difficult to demonstrate, but here again the ulcer may be recognized "en face" through the air-filled body of the stomach.

TABLE I.—GASTRO-INTESTINAL BLEEDING (33 CASES)

Positive findings (21)

Esophageal:	Hernia + ulcer 1, dilated oesophagus and retention of dye 1
Gastric:	Peptic ulcer 4, probable ulcer 2
Stomach:	Ulcer 1
Duodenal:	Ulcer 9, probable ulcer 3

Negative findings (12)

9 patients on follow-up settled on conservative treatment.
3 patients positive on later investigation: 1 Gastric ulcer,
1 acute gastritis, 1 prepyloric ulcer

considerable attention has been paid to the ward barium meal where the examination is carried out at the patient's bedside after the patient has ingested a quantity of barium sulphate. This examination can reveal only the grosser lesions; an examination with adequate facilities in an X-ray department, if necessary while the patient is being transfused, probably causes no more



FIG. 4.

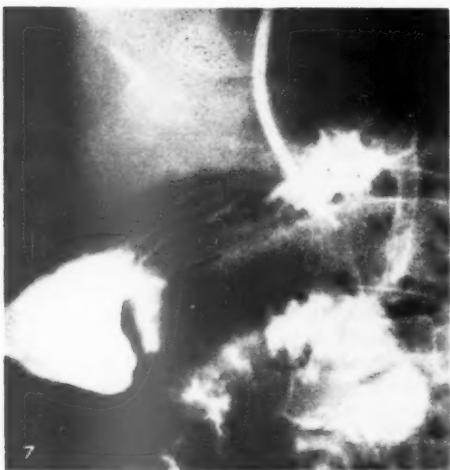


FIG. 5.

Figs. 4 and 5.—Showing the appearances of a duodenal (Fig. 4) and of a gastric (Fig. 5) ulcer seen "en face"—the double density appearance is clearly seen.

Blood clot.—The presence of blood in the stomach with clot formation has been put forward as a cause of difficulties in diagnosis. In our experience this has not been so and we have not found any marked difficulties in diagnosis due to blood clot. In the early stages of the investigation an isolated case caused some confusion in diagnosis when a blood clot was shown to be adherent to the stomach wall and presumably



FIG. 6.—An external fistula occurring after a partial gastrectomy associated with an extensive leak into the peritoneal cavity.

overlying an ulcer crater. Usually, the outline of the blood clot is smooth and well defined and can therefore be differentiated from a new growth. In other instances the blood clot has been shown to prolapse through the pylorus.

Perforations and leaks.—Table II shows the

TABLE II.—POSSIBLE PERFORATIONS (20)

Positive findings (14)		
Duodenal ulcer + leak	...	3
Active duodenal ulcer	...	11
Negative findings (6)		
No diagnosis	...	5
Cholelithiasis	...	1
All diagnoses confirmed at operation or condition settled on conservative treatment.		

cases of suspected perforation investigated by oral contrast medium. In the positive cases where a leak has been shown, the outline taken by the dye indicates the path of infection and the fistulous communication through the perforation has been readily demonstrated. We have limited our investigation of cases of duodenal perforation to those where the clinical diagnosis was indefinite or where the plain films did not show evidence of pneumoperitoneum. Where a pneumoperitoneum was demonstrated the investigation by contrast medium was not performed but there is no doubt, if this investigation were performed more frequently the percentage of cases showing perforation would rise. It seems possible that patients may be divided into those showing perforation with indication for immediate surgery and the second group where no perforation is seen. The latter could be treated conservatively and, as Table II shows, in the vast majority the symptoms were due to deep penetration by the ulcer crater and not to any leak.

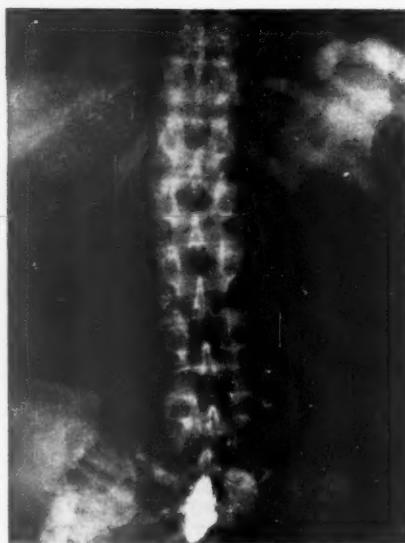


FIG. 7A.—Plain film after partial gastrectomy showing a single distended loop of small bowel. The erect film showed no evidence of fluid level.

Leaks from anastomotic lines are relatively easy to demonstrate, and pleuro-esophageal fistulae and fistulae from anastomotic lines at the sites of partial gastrectomy were readily demonstrated by the administration of oral contrast medium. The outlines of the fistulous tracks prove of considerable assistance in treatment (Fig. 6). In our investigations of post-operative gastrectomies we have been impressed by the usefulness of the oral contrast medium in demonstrating the integrity of the suture line.

Intestinal Obstructions

The extensive use of X-rays in the diagnosis of intestinal obstruction is testimony to its value in the management of these clinical states, and at the Royal Infirmary of Edinburgh the method is routine in the investigation of any acute abdomen.

In many instances the diagnosis can be made with considerable assurance on some classical appearances; where such accuracy of diagnosis is impossible, the administration of oral contrast medium may demonstrate the nature and anatomical site of the affected loop. The usefulness of oral contrast medium in intestinal obstruction is especially seen in those cases of high no-gas obstruction, where it is the only means of making a radiological diagnosis. Such cases, which occur most frequently after gastrectomy, are notoriously misleading on plain films (Figs. 7A, B). The high site of the obstruction results in the failure of any gas to pass into the



FIG. 7B.—Same patient after the administration of Gastrograffin, demonstrating an obstruction in the end part of the duodenum due to pancreatitis.

alimentary canal and consequently excludes the formation of fluid levels (Figs. 7A, B). We have used the oral medium to determine whether any true mechanical obstruction is present as opposed to an ileus and in such patients we have been able to demonstrate the absence of complete obstruction. A word of caution must, however, be raised in relation to vascular lesions. The vascular occlusions merely produce a localized area of paralytic ileus and in such cases the contrast medium can be shown to pass through the affected area quite slowly. There is a risk that a mistaken diagnosis of ileus without due regard to the seriousness of the vascular obstruction will be made.

Pancreatic Lesions

Acute pancreatitis may cause difficulty in diagnosis when the clinical picture is incomplete or when the laboratory studies of serum amylase or urinary diastase fail to give positive findings. In such patients the administration of oral contrast medium may considerably assist in the diagnosis. Segmental pancreatitis involving the tail or body of the pancreas may be demonstrated by changes in the duodeno-jejunal flexure and the retrogastric portion of the stomach. The changes in the duodeno-jejunal flexure correspond to the similar changes seen in the C-curve of the pancreas in inflammatory lesions in the head of the pancreas, namely oedema and widening of the mucosal folds and fixity of this



FIG. 8.



FIG. 9.

Figs. 8 and 9. Prone and lateral films of a patient with subacute pancreatitis where the plain films showed no abnormality and where no mass was palpable on clinical examination. The films demonstrate the gross forward displacement of the stomach by the pancreatic inflammatory mass.

Figs. 1-5, 8 and 9 are reproduced by kind permission of the Editor of the *British Journal of Radiology*.

portion of the small bowel. It is important when lesions of the body or the pancreas or tail are suspected that a careful examination of the duodeno-jejunal flexure be undertaken. In other instances of subacute pancreatitis, demonstration of the inflammatory tumour mass behind the stomach may be clearly seen by the forward displacement of the contrast-filled stomach (Figs. 8 and 9).

Cholecystitis

Plain radiography of the abdomen has proved disappointing in the investigation of acute cholecystitis and in the demonstration of calcified gall-stones. In a series of 200 consecutive cases of acute abdomen admitted to the Royal Infirmary of Edinburgh in the first six months of 1959, only 25% of cases of acute cholecystitis admitted showed stone formation on the plain film. In 75% of cases no suggestion as to the nature of the acute episode could be made from the plain films. It is equally agreed that a differentiation of acute obstructive from acute non-obstructive cholecystitis is of paramount importance. For this reason we have used intravenous contrast medium to differentiate between the acute obstructive and non-obstructive cholecystitis. The advent of intravenous Bili-grafin has enabled the investigation to be carried out during the acute stage with little disturbance

to the patient. By this means patency or otherwise of the cystic duct can be recognized within two hours of the injection. Although it is theoretically possible for an acutely inflamed gall-bladder to fill with Bili-grafin, as no concentration of dye occurs in the gall-bladder, this seldom occurs. Following the injection of 20 c.c. of Bili-grafin Forte, the following findings may be established:

(1) A complete failure to display either the gall-bladder or the extra-hepatic ducts. In such a patient, it may be concluded that the liver has failed to concentrate the dye sufficiently to enable a shadow to be seen and no opinion on the state of the gall-bladder can be expressed. A lateral film may demonstrate the dye in the colon mixed with faeces indicating that concentration of the dye is relatively poor and diluted.

(2) The liver readily excretes the dye. The extra-hepatic biliary passages are clearly seen and the cystic duct and gall-bladder fill up normally. This indicates a normal biliary system but as already stated does not wholly exclude the possibility of an acutely inflamed gall-bladder.

(3) The extra-hepatic ducts fill out normally but the gall-bladder fails to fill when serial films of the gall-bladder have been taken. At two hours, this usually indicates an obstruction of the cystic duct, but under certain conditions the gall-bladder may fill at a later stage, and for this reason if no filling occurs up to two hours we prefer to take a subsequent film at four hours.

In one patient in this series, despite the non-filling of the gall-bladder and the diagnosis of an obstruction of the cystic duct, no stones were found in the gall-bladder. Presumably in these patients the oedema of the mucosa and the general swelling of the duct causes an obstruction of the cystic duct. In our series one patient with segmental pancreatitis also demonstrated a normal extra-hepatic biliary tract but no visualisation of the gall-bladder; acute obstructive cholecystitis was diagnosed but laparotomy revealed a segmental pancreatitis involving the tail and body of the pancreas. Why this condition should result in non-filling of the gall-bladder is not known.

Urinary Tract

Extensive series of investigations have been carried out on the use of intravenous urograms in the detection of stone formation in the urinary tract. Undoubtedly, a stone lodged in the ureter causes suppression of excretion of dye from that kidney and although a dense nephrogram shadow is obtained in many instances the demonstration of a stone is disappointing. In a series of 200 consecutive acute abdomens admitted to the Royal Infirmary in the early part of 1959, 16 were potential renal lesions and in these stone formation was only seen on the

plain film in 2. These figures confirm that plain radiography is disappointing in demonstrating ureteric calculi and when errors of interpretation due to gas and meteorism of the bowel are also considered, the value of plain radiography is further diminished.

Table III demonstrates the features we have found of value in the intravenous pyelogram.

TABLE III.—NON-OPAQUE STONE X-RAY FEATURES

- (a) The prolonged nephrogram on the affected side.
- (b) The delay in the appearance of the pyelogram.
- (c) The distension of the renal pelvis and the ureter as far as the site of obstruction of the case is followed for a sufficient interval.

The Use of Contrast Media in the Acute Abdomen [Summary]

By P. G. KEATES, M.D., M.R.C.P., D.M.R.D.

Leeds

THE ward barium meal is used routinely in the investigation of haematemesis and melena at the Leeds General Infirmary (Cantwell, 1960, *Clin. Radiol.*, 11, 60) and a review of 200 cases shows that it is possible to make a correct diagnosis in 80% by this method. Two films are exposed in the ward without use of screening facilities and with minimal disturbance of the patient, and by using 5 oz of barium suspension followed by a mouthful of barium paste the oesophagus, stomach and duodenum are demonstrated.

A variety of lesions have been shown successfully but the diagnosis of carcinoma of the stomach was unsatisfactory and the diagnosis of an acute peptic ulcer could only be made by exclusion of other conditions.

Intravenous pyelography is used as a regular, immediate procedure in patients with renal colic and the results will be reported fully elsewhere. Intravenous pyelography gives significant find-

ings in 95% of patients with calculous renal colic. 25% of stones causing colic are nonopaque and the "acute intravenous pyelogram" is the only method by which their presence can be demonstrated radiologically.

The examination is carried out without prior preparation at any time of day, and the inconvenience to the department of this emergency work (100 cases a year) is more than repaid by the saving of subsequent negative "cold" intravenous pyelograms. The method, which has proved of great value in the clinical management of the patient with this condition, has indicated that complete suppression of function of the affected kidney seldom occurs, but films over a period of several hours may be required to show that the kidney is slowly excreting, and to demonstrate the site of obstruction.

[A fuller account of this paper will appear in *Clinical Radiology, The Journal of the Faculty of Radiologists*.]

Meeting

February 19, 1960

100 Consecutive Cases of Dysphagia: Some Problems in Diagnosis [Summary]

By G. OSBORNE, M.R.C.P., D.M.R.D., P. T. SAVAGE, F.R.C.S., and S. L. STRANGE, F.R.C.S.Ed., D.T.M.

London

THIS paper is based on 100 consecutive cases of dysphagia referred to one of the authors (G. O.) for radiological examination. An analysis of the series is shown in Table I.

Among the problems encountered in diagnosis were the following:

(1) The simulation of cardiospasm by carcinoma arising in the upper third of the stomach and extending submucosally into the lower

TABLE I.—100 CONSECUTIVE CASES OF DYSPHAGIA

Carcinoma of oesophagus	11
Malignant tumour of stomach	19
Cardiospasm	6
Carcinoma of bronchus	4
Hiatus hernia	10
sliding hernia	4
sliding hernia with peptic oesophagitis	27
sliding hernia with innocent stricture	9
para-oesophageal hernia	4
sliding hernia with malignant stricture (listed with cases of carcinoma of oesophagus and stomach)	7
Following operations on the stomach	4
Miscellaneous causes	8
No cause for dysphagia found	21

oesophagus. The main growth in the stomach may escape detection at the barium meal when the degree of hold-up prevents enough barium entering the stomach at a time for its adequate examination.

(2) The difficulty in distinguishing between intrinsic growths of the oesophagus and extrinsic growths, such as carcinoma of the bronchus, which compress the oesophagus from without. The radiological appearances may be identical and this difficulty indicates the need for bronchoscopy in the investigation of some cases of dysphagia.

(3) The difficulty in making the distinction between the benign stricture of peptic oeso-

phagitis and a malignant stricture associated with a hiatus hernia. Filling defects and irregularities of the stricture may point to the correct diagnosis but oesophagoscopy and biopsy are essential here as in the investigation of most cases of dysphagia.

The 21 cases in which no cause for the dysphagia was found and the cases of apparently uncomplicated sliding and para-oesophageal hiatus hernia were followed up for long enough to exclude a malignant lesion.

[This paper will be published in full in *Clinical Radiology, The Journal of the Faculty of Radiologists*.]

Benign Stricture of the Lower Oesophagus

By N. R. BARRETT, M.Chir., F.R.C.S.

London

I PROPOSE to discuss a few states that are said to cause benign strictures in the lower oesophagus. The postcricoid region of the gullet will be excluded because the pathology of strictures there is more nebulous. At this time I define the word "stricture" to mean a permanent pathological narrowing, and the "oesophagus" to be that part of the alimentary canal between the cricopharyngeal sphincter and the cardia.

We can assume that within these definitions there is no doubt as to the authenticity of strictures due to corrosives, to dermatomyositis, to reflux and to new growths. Opinion may be reserved, or even sceptical, as to the part played aetiologically by such diverse conditions as typhoid fever, syphilis, rheumatoid arthritis and avitaminosis, &c. And I shall leave the reader to form his own opinion about such exotic entities as "emotional crises" as a cause of persistent obstruction.

Fact or Fiction

The ideas embodied in this paper arose as a result of trying to differentiate and understand a number of common conditions that occur in the oesophagus, and that are often credited with causing strictures of the type I have defined.

Spasm.—One has only to read Johnstone's writings to realize that radiologists see a variety of transient constrictions in this region that they do not understand. These constrictions are sometimes considered to be due to "spasm", and persistent spasm is said to produce permanent changes in the wall of the oesophagus. This idea is often backed up by the statement that lower oesophageal strictures "bear a striking similarity to the irreversible changes in the cricopharyngeus muscle following long-continued spasm".

I am not convinced that spasm can produce a pathological stricture of the oesophagus; there is always, in my experience, a more logical explanation of the circumstances. It is agreed that congestion and oedema, when added to a persistent pathological stenosis, may accentuate dysphagia or make swallowing impossible.

It has been proved by intra-oesophageal pressure readings that *generalized oesophageal spasm* exists, but Creamer (1959) tells me that in more than 1,000 consecutive investigations, done upon patients suffering from all manner of oesophageal ailments, he has not detected *local muscle spasm*. The significance of an observation such as this may be no more than that it widens the gaps in knowledge between radiology and pressure tracings.

Conditions such as achalasia were formerly considered as proof that the lower oesophagus can produce a stricture due to permanent spasm, but nobody accepts this view to-day.

Strictures are said to result from spasm that is secondary to vagotomy, cholecystitis, duodenal and gastric ulcer; but in my experience these are associated with oesophagitis due to reflux, and it is reflux that produces the permanent stricture.

Persistent spasm is also said to cause "giant muscular hypertrophy"; but some strictures of this type have been excised, and the lesions are found to be benign new growths of the muscle coats of the oesophagus and not spasm. Myomatosis of this type exists in two forms; small local muscle tumours can produce the appearances of a benign stricture radiologically; and diffuse myomatosis accounts for some cases diagnosed as "long strictures", for some cases of corkscrew oesophagus and some of multiple segmental spasm (Barsony-Teschendorff syndrome). It is

my guess that local spasm will cease to be considered as an aetiological precursor of permanent oesophageal stricture.

"Congenital strictures."—Whenever an annular stricture of the oesophagus, of unknown aetiology, is revealed radiologically, there is a probability that it will be called "congenital". This word "congenital" matters because it purports to explain everything and make treatment straightforward. In my experience annular congenital strictures do not occur. It is accepted that various types of tracheo-oesophageal fistula exist, as well as complete oesophageal atresia. In the latter the blind ends have sometimes been described as being 10-15 cm apart, and connected by a strand of solid tissue that, histologically, was muscle.

If there is such an entity as a congenital annular oesophageal stricture it would, presumably, take one of two forms. It would either be a diaphragm formed of mucous membrane or a localized web of overgrown muscle. The two might be combined. With regard to the former one must admit the possibility because, according to Johns, the foregut in the 3-mm embryo becomes occluded by proliferation of the columnar epithelium that lines it, and it is recanalized later on. This might lead to residual epithelial diaphragms. But the idea that congenital atresia of any part of the intestine is due to failure of recanalization (as was originally postulated by Tandler in 1902) has recently been challenged by Louw (1959), and numerous other authorities, who feel that local infarction, leading to a length of aseptic necrosis, is a more likely explanation. "Congenital stricture" of the oesophagus has not, as yet, been considered comparable to duodenal atresia.

"Lower oesophageal webs and rings."—In 1953 Inglefinger and Kramer described the radiological appearances in 6 patients who had complained of dysphagia and in whom they demonstrated by special techniques contractile rings in the lower oesophagus. They regarded these "strictures" as variable in position and concerned in some way with irregular peristalsis; nothing abnormal was found at oesophagoscopy. The lower part of the oesophagus is, however, notoriously difficult to be dogmatic about radiologically; and it is not the easiest place to be sure about at endoscopy. It might be true that the surgeons who looked at the gullets in these patients did not see everything that was there.

In the same year Schatzki and Gary (1953) described concentric narrowings in the lower oesophagus that "sometimes caused dysphagia". They stated that these were constant in position and shape and due to permanent pathological lesions in the wall of the oesophagus. They

assumed that the anomalies were congenital and this opinion was confirmed by Bonilla and Bowers (1959) and by Bugden and Delmonico (1956) who operated upon some patients and found cones of fibromuscular tissue obstructing the lumen of the oesophagus. There was no sign of inflammation in these patients and the mucous membrane below the obstructions was stated to be normal, and appeared "oesophageal" to the naked eye. Harken operated upon one of Schatzki's cases and found that the web was immediately proximal to a sliding hiatal hernia. These surgeons did local excisions or plastic operations upon the webs and claimed excellent results. They did not challenge the conventional explanations, either as to cause or treatment.

The Nature of Benign Annular Stricture

I submit that practically every case of benign, annular stricture of the oesophagus is due to reflux oesophagitis, and that this should be assumed to be the cause until there is proof to the contrary. To substantiate this statement it will be necessary to make some observations about strictures that are known to have been caused by reflux oesophagitis; to refute current explanations of the various pathological conditions described above, and to adduce some positive evidence.

Points about strictures that complicate reflux.—Strictures that complicate reflux are, in their extremes, of two types that, at first glance, seem to be different lesions.

Type I: The usual result of prolonged digestive inflammation due to reflux is that a mass of fibromuscular tissue grows in the wall of the oesophagus, and by its bulk and contraction occludes the lumen. This stricture originates in the lowest fringes of the squamous epithelium and spreads upwards in the gullet producing a palpable fixed lump that can simulate carcinoma. *This type of stricture does not concern us.*

Type II is less common. The stricture is annular and practically confined to the submucosa. The mucous membrane and the muscle walls of the oesophagus are intact, and there may be no evidence at the time of active acute or chronic inflammation.

Both varieties sometimes occur immediately above a sliding hiatal hernia; and it has been conceded in the literature that *some* rings, webs, and congenital strictures are of this annular type. But all surgeons are not aware that a *ring stricture* surmounting a sliding hiatal hernia can be due to that hernia: if they were, local operations on the stricture and dilatations would not be described as the treatments of choice (Benedict and Gillespie, 1954).

Current arguments in favour of accepted views.—Whilst it is admitted that a ring stricture can

complicate a sliding hiatal hernia, how can one account for such a stricture in a patient who has no hiatus hernia, and who radiologically has a normal oesophagus below the obstruction, and no reflux from the stomach? And even if a small hernia is present these web-like strictures are often several inches above the oesophagogastric junction. Moreover the oesophagoscopist generally reports that the upper surface of the stricture shows no evidence of oesophagitis: the mucous membrane is normal. The stricture cannot, therefore, be due to oesophagitis.

Contrary arguments.—These criticisms are dispelled by the fact that a *ring stricture may complicate a lower oesophagus lined by columnar epithelium*, exactly as it may a sliding hiatal hernia.

Before enlarging upon this point, the following facts about a lower oesophagus lined by columnar epithelium must be emphasized:

(1) The change-over in the epithelium can occur at any level in the oesophagus, though it is usual in the lower third.

(2) The condition can exist in conjunction with a sliding hiatal hernia (Allison and Johnstone, 1953).

(3) If there is no sliding hiatal hernia the gullet below the obstruction exactly simulates oesophagus radiologically.

(4) The mechanism that prevents reflux is *never* at the junction of the squamous and columnar epithelia in these cases; if it exists, it is where the oesophagus appears to join the stomach below the diaphragm.

(5) The lesions that develop at the junction of the two mucous membranes are the same as those that complicate sliding hiatal hernia. Their treatment may be different.

(6) The acid-pepsin that does the damage in these cases comes chiefly from the columnar-lined oesophagus, and not necessarily from the stomach.

Surgeons pay lip service to the idea that the lower oesophagus may be lined by columnar epithelium; but they generally hasten to add that they have never seen such a case. The reason is that they do not recognize these lesions when they see them. At one time last year there were 3 such patients under my care at the same moment; but the nature of their strictures was not immediately acceptable to my colleagues.

It will be appreciated that, unless the stricture is excised and examined histologically, there is only one thing that will suggest its cause—namely biopsy sections of the epithelium taken *above* and *below* it. If the stricture has squamous epithelium above it and columnar epithelium below it, reflux oesophagitis is strongly suggested as the aetiological cause.

In reading through the literature I cannot find any recommendation that distal mucosal biopsies should be taken; and even when a stricture has been excised (Bonilla and Bowers, 1959) the histology of the lesion is often misleading because a *transverse* section is all that is published. I advocate that the relevant sections are those cut *along* the oesophagus and through the stricture, so that one can examine what is happening above and below the lesion, without assuming that the epithelium below is the same as it is above. It is impossible to be sure of the nature of these epithelia merely by opening the oesophagus and looking with the naked eye.

I have now operated upon and excised 6 benign annular strictures and the histological findings were identical in every case. All had been diagnosed and treated as "congenital" obstructions, and the radiological findings were in line with this idea. The oesophagus below these strictures looked normal radiologically, and it had not occurred to anybody that the epithelium was columnar. In fact all were suffering from fibrous, submucosal, strictures that looked like webs and were situated at the change-over in the epithelia.

I admit that I do not know how these webs develop. I postulate that in early life the child, having a lower oesophagus lined by columnar epithelium, develops oesophagitis, and that this results in a ring stricture comparable to that occurring at the base of an appendix after an attack of catarrhal inflammation. Once the stricture has formed, it looks like a diaphragm set across the lumen of the gullet and perforated by a small central aperture. Through this hole the child can swallow liquids and unless the lumen is critically small, solids may be taken without undue difficulty. As the child grows, dysphagia may be manageable by attention to the details of eating and the patient may live in reasonable comfort until, or unless, some object impacts.

If we now consider events upon the lower side of the stricture, we can appreciate that although it is perforated centrally and fluid passes down when the patient is erect, it could have the effect of practically blocking reflux when the patient is recumbent—at least till the contents of the lower oesophagus have accumulated above the lip of the hole, and then it is probably just as easy for the secretions to flow down into the stomach as to rise up in the mediastinum. The higher the lesion the less the negative pull of inspiration encourages regurgitation into the oesophagus above the stricture.

The stricture is, in fact, nature's way of protecting the squamous epithelium above it, and this is demonstrated by the normality of the

proximal mucous membrane. The idea that such a stricture is due originally to reflux is not upset by the observation that, after excision or dilatation, the dysphagia is relieved. We know that the usual massive stricture that complicates reflux, and that is likely to result from these treatments, may take years to form. We also know that long, critical, follow-ups are not always made. I have oesophagoscoped 2 patients soon after dilatation of so-called non-inflammatory, "congenital", strictures and have found active oesophagitis. The patients were pleased by what had been done for them. I was not.

In conclusion, the idea underlying this paper is that a number of supposedly different conditions, namely "congenital oesophageal strictures", "oesophageal webs, and rings", and "annular peptic strictures" are, for practical purposes, one and the same thing. They are organic strictures due to reflux oesophagitis. This has not been accepted in the past because surgeons have not realized that the lower oesophagus is quite commonly lined by columnar epithelium, and that annular peptic stricture can complicate this anomaly exactly as it does a sliding hiatal hernia.

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Motor Mechanisms of Dysphagia [Summary]

By B. CREAMER, M.D., M.R.C.P., and J. W. PIERCE, M.D., M.R.C.P., D.M.R.D.
London

THE use of combined pressure measurements and cine-radiography has given a clear picture of the normal mechanisms of swallowing. Pharynx, cricopharyngeal sphincter, oesophagus and gastro-oesophageal junction are involved in a single peristaltic action with co-ordinated relaxation of the sphincters. Dysphagia may be produced by inco-ordination of the peristaltic wave or sphincters in any of these four sites.

Absence or gross weakness of pharyngeal propulsion has been seen in myopathy and certain vascular lesions of the mid-brain. This produces a picture of retention of barium in the pharynx that may be indistinguishable from that caused by a failure of the cricopharyngeal sphincter to relax. This is again produced by cerebrovascular accidents, usually a severe form of thrombosis of the postero-inferior cerebellar artery. These two physiological upsets can only be distinguished by pressure measurements.

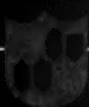
The principal inco-ordination of the oesophagus

is diffuse spasm, where the peristaltic wave is replaced or obliterated by abnormal, simultaneous contractions of the lower half which are vigorous and often repetitive. These contractions cause the radiological picture of a rippled or frankly corkscrew oesophagus where barium is trapped and not propelled. In this condition the gastro-oesophageal junction relaxes normally and offers no obstruction.

Achalasia of the cardia is characterized by a failure to relax the gastro-oesophageal junction and also by a complete loss of usual oesophageal peristalsis. Abnormal oesophageal contractions are present but these fail to obliterate the lumen, a distinguishing point from diffuse spasm, for where the oesophagus is not dilated these conditions may cause a similar radiological picture.

The physiology of these conditions was illustrated by pressure recordings and cine films of barium swallows.

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February 10, 1960

DISCUSSION ON SQUAMOUS CELL CARCINOMA OF THE ANUS AND ANAL CANAL

Mr. W. B. Gabriel (London):

When I previously addressed the Section on this subject (Gabriel, 1941), my analysis was based on 55 cases admitted to St. Mark's Hospital during the nineteen-year period 1922 to 1940 (Table I). I have now, with my colleagues' permission, studied the 96 cases of squamous carcinoma admitted to St. Mark's during the next fifteen-year period, 1941-55. In addition I have brought in 21 other cases under my care elsewhere during this period, making a total of 117 cases, as follows:

Carcinoma of the anus: 30 cases (25 males, 5 females).

Carcinoma of the anal canal: 87 cases (46 males, 41 females).

On comparing the two sets of figures shown in Table I it seems fair to make the following

TABLE I.—SQUAMOUS CELL CARCINOMA OF THE ANUS AND ANAL CANAL

	1922-1940			1941-1955			Total
	Males	Females	Total	Males	Females	Total	
Squamous carcinoma of anus ..	24	5	29	25	5	30	
Squamous carcinoma of anal canal ..	3	23	26	46	41	87	
Total ..	27	28	55	71	46	117	

comments: (1) The incidence and sex distribution of squamous carcinoma of the anus has remained constant in the periods studied, the disease being five times more common in men than in women. (2) There has been a threefold increase in the incidence of squamous cell carcinoma of the anal canal. (3) In the earlier period, females with squamous carcinoma of the anal canal greatly outnumbered the males, whereas in the 1941-55 period males outnumbered the females (46 to 41).

Later I will indicate the improved results of treatment by local excision for carcinoma of the anus instead of interstitial radium needling and radical combined excision for squamous carcinoma of the anal canal instead of perineal excision.

Although they arise in adjacent parts squamous cell or epidermoid carcinoma of the anus and squamous cell carcinoma of the anal canal are extremely different and, except that they are both malignant in varying degrees, they have little in common whether considered from the clinical, surgical or histological aspects.

Predisposing Conditions

It is difficult to explain the 5 to 1 preponderance of males over females in squamous carcinoma of the anus; although the following conditions may be considered they do not seem to provide an adequate answer to this question.

Pruritus ani.—Severe degrees of chronic anal pruritus are more common in men than in women and habitual rubbing and scratching might, one would think, initiate a localized carcinoma of the anus. But of the dozens of cases of pruritus ani seen in out-patient clinics few develop squamous carcinoma of the anus. Fig. 1 illustrates what

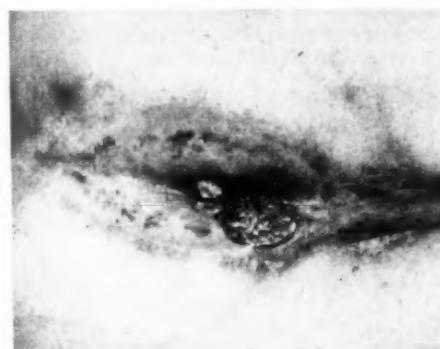


FIG. 1.—Squamous cell carcinoma of the anus with secondary pruritus ani.

appears to be a chronic pruritus ani with a localized carcinoma of the anus in the left anterior quadrant in a man aged 63. Yet the history is a complaint of bleeding and pain of one month's duration, with no mention of anal pruritus, so it would seem likely that the skin changes in this case were secondary to the discharge from the anal carcinoma and not the cause of it.

Leukoplakia of the anus (Fig. 2) occurs exclusively in men over the age of 60 and, however unpleasant some of the indolent traumatic ulcers may appear, with raised somewhat indurated margins, my experience is that these patients do not develop carcinoma of the anus. I have records of 10 of these cases who have been under observation for periods up to twelve years and in no case was there any malignant development.

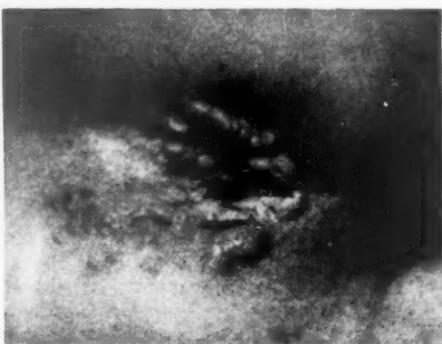


FIG. 2.—Male aged 69 with chronic leukoplakia of the anus. There was an indolent chronic ulcer on the left side and the condition remained essentially unchanged during the ensuing nine years with no malignant change.

Simple papilloma.—The common anal wart or condyloma acuminatum shows no tendency to become malignant and it is only rarely that a massive papilloma in the anal region may in part undergo malignant change. For example (Fig. 3), a man aged 67 had anal warts for eight years



FIG. 3.—Extensive papilloma of the anus of eight years' duration with a localized squamous carcinoma in the right posterior anal quadrant. This was excised locally with cutting diathermy and the patient has been free from recurrence for four years. The right posterior hemorrhoid which is seen presenting was ligated and excised in the course of operation.

and finally developed a keratinizing squamous cell carcinoma in the right posterior quadrant. This was excised locally in January 1956 and there was no recurrence up to December 1959.

Long-standing fistula.—It is a commonplace that a long-standing fistula may undergo malignant change and in the St. Mark's series 1941-55 there were 2 such cases (1 male, 1 female) where fistulae had been present for fourteen and fifteen years respectively.

Squamous cell replacement (Figs. 4 and 5).—The acquired squamous cell overgrowth or replacement over the original columnar epithelium of prolapsing hemorrhoids might provide the starting point for a squamous cell carcinoma and some of the sections I have examined show evidence of superficial ulceration at the junction of the two types of epithelium with some inflammatory changes beneath. In the St. Mark's series just mentioned there were 2 cases where small squamous carcinomas developed over the lower pole of the right anterior hemorrhoid. Both were excised locally: one was $\frac{1}{2}$ in. in diameter and proved to be of low malignancy; no recurrence followed and the patient survived for seven years. The other was 1 in. in diameter and



FIG. 4.

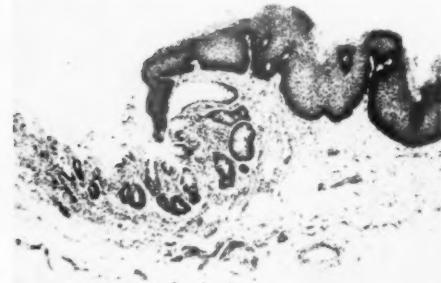


FIG. 5.

Figs. 4 and 5.—Squamous cell replacement over the columnar epithelium of prolapsing hemorrhoids. (Low power.)

was of a high grade of malignancy; on this account a synchronous combined excision of the rectum was carried out a month later. After an interval of two years metastases developed in both groins and a block dissection left and right was required (1 positive gland on each side). The patient died of recurrence fourteen months later.

Diagnosis

A typical localized squamous carcinoma of the anus, with its sharply defined raised indurated and everted edge, is generally sufficiently obvious to warrant local excision without a previous biopsy (Fig. 6).

When the lesion is more diffuse, as in Fig. 7, it may at first be difficult to say if we are dealing with a carcinoma of the anus or of the anal canal, or indeed it might be a carcinoma of the rectum extending downwards. A finger should be passed into the anal canal and if it feels rough and ulcerated then clearly the case is not one of carcinoma of the anus and a biopsy will show if the growth is squamous or columnar cell. This particular case, a woman of 56, had a differentiated squamous cell carcinoma of the anal canal and was treated by a perineo-abdominal excision together with a wide removal of the buttocks and posterior vaginal wall, B case. She has remained well for more than nine years and no spread has taken place to the groins.

When we meet an ulcerating neoplasm in the anal canal a biopsy is required for a precise diagnosis and examination under anaesthesia is often a useful if not an essential preliminary procedure, not only to get satisfactory fragments for biopsy but to assess operability. This applies particularly in the male when the ulcerated growth is situated anteriorly and one likes to form



FIG. 6.—Differentiated squamous cell carcinoma of left lateral anal margin. This was excised with cutting diathermy (June 1951) without previous biopsy. Patient alive and well for the ensuing eight and a half years without indication at any time for a block dissection of the groin.

an estimate whether the growth is likely to come off the urethra and prostate kindly or not.

If the growth, as commonly happens, is of the anaplastic variety it may be a problem for the pathologist to say if it should be considered to be a squamous cell or columnar cell lesion. But from a practical point of view it makes little difference and the treatment will be the same, namely by a radical combined excision. In 7 cases in this series a growth in the anal canal has proved to be squamous cell in its lower part and adenocarcinoma in the upper part; this is a reasonable and not unexpected finding and metastases of both varieties of growth can occur in the haemorrhoidal lymph nodes.

I should here offer a warning about primary chancres of the anus because there appears to be an increased incidence of this condition. Between November 1958 and February 1959 I saw 3 cases and the last one in a man aged 44 was the most deceptive. He presented an ulcerated anal lesion posteriorly (Fig. 8) and in addition there was a small hard gland in the left groin which was not tender. I thought that this fact together with the patient's age contraindicated a venereal lesion. Fortunately, however, I decided to have the tests done before submitting him to surgery and within twenty-four hours the dark ground search for spirochaetes proved to be positive, and both W.R. and Kahn tests were strongly positive.

If a lesion in the anal canal appears to be dusky in colour and there is a possibility of it being a malignant melanoma, biopsy should be deferred until the patient has been hospitalized. Then no doubt a frozen section in the theatre can be organized and if positive a radical operation can



FIG. 7.—Female aged 56 with extensive squamous cell carcinoma of the anal canal extending down to the anus and perianal region. Perineo-abdominal excision (March 1950) and patient has survived for nine and a half years. There has been no indication during this period for a block dissection of either groin.

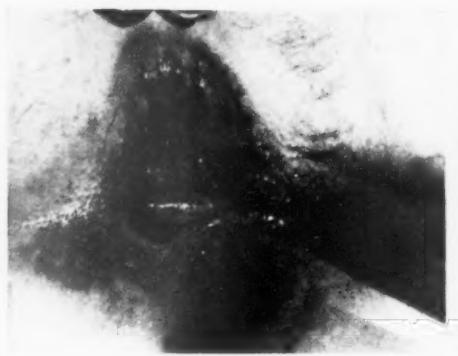


FIG. 8.—Primary chancre of the anus in a male aged 44. There was a hard gland in the left groin and the resemblance to a squamous carcinoma was very close.



FIG. 9.—Tuberculous ulcer of the anus in a male aged 33.

be proceeded with at once. This opinion is based on an unfortunate case I had ten years ago when a delay occurred after a biopsy on a melanoma and it seemed likely that rapid metastasis might have been initiated by the biopsy.

There is not, as a rule, any difficulty in diagnosing tuberculous ulceration of the anus (Fig. 9) and except for those due to a milk-borne bovine infection the condition is secondary to active pulmonary tuberculosis so that all we have to do is to X-ray the chest and examine the sputum. In this case the patient had bilateral active pulmonary tuberculosis with cavitation in the right apex. In addition I snipped off a small projecting nodule of granulation tissue and the section confirmed a tuberculous lesion.

Prognosis

In my experience carcinoma of the anal canal is a much more dangerous and serious disease than carcinoma of the anus.

Some five years ago Dr. Cuthbert Dukes and I examined the histology of this series and on a histological basis we classified them into two main groups—squamous cell and basal cell, each group being divided into (1) differentiated, (2) anaplastic. These groups are discussed together because so far as the anal canal is concerned it seems likely that the degree of differentiation is of greater importance from the surgical aspect than slight differences in the histological picture depending on the level of origin of the growth.

Of the 87 carcinomas of the anal canal 66 or rather more than two-thirds were anaplastic, whereas of the 30 carcinomas of the anus only 10 or one-third were of the anaplastic variety. This difference is reflected when we examine operability and the results of treatment.

Of the carcinomas of the anal canal 21 or approximately one-quarter were advanced locally

and were inoperable either owing to the local state or on account of metastases in the lungs or liver. Table II shows that 19 out of 21 were anaplastic.

TABLE II

	Operable		Inoperable		Total
	Differentiated	Anaplastic	Differentiated	Anaplastic	
Carcinoma of anal canal	19	47	2	19	87
Carcinoma of anus	19	9	1	1	30

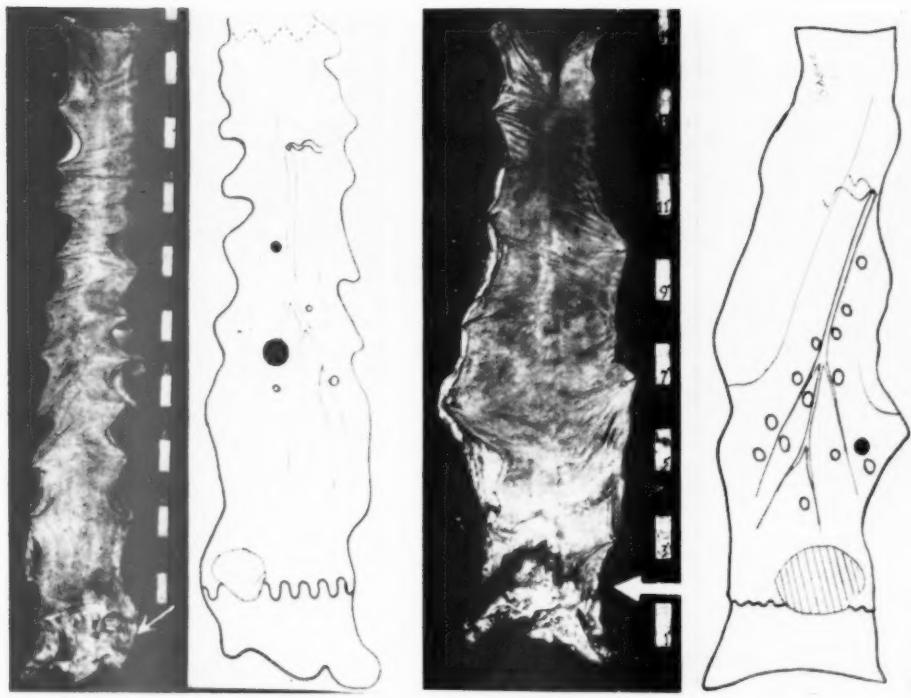
On the other hand 28 out of 30 carcinomas of the anus were operable and were resected mostly by local excision and only 2 were inoperable. The one inoperable differentiated carcinoma of the anus was a case arising in a fistula of fifteen years' duration which had extensively invaded the buttocks (Table II).

Treatment

Carcinoma of the anal canal.—During the first five years (1941-45) of the fifteen-year period reviewed most of the operable cases were treated by colostomy and perineal excision, but since 1946 radical combined excision (synchronous or perineo-abdominal) has been the method of choice.

Of 67 cases treated by radical operation there were only 5 A cases (7.5%) which is exactly half the usual expectancy of A cases in adenocarcinoma of the rectum. The remaining 62 cases were almost equally divided between the B and C groups. In view of the frequency of spread to the superior haemorrhoidal lymph nodes (Fig. 10),

FIG. 10.—Four examples of anaplastic squamous cell carcinomas of the anal canal removed by radical combined excision. These were all C cases with lymph node involvement. Discontinuous lymphatic spread and also venous involvement are evident in D. The patient (A) had previously received deep X-ray therapy. →



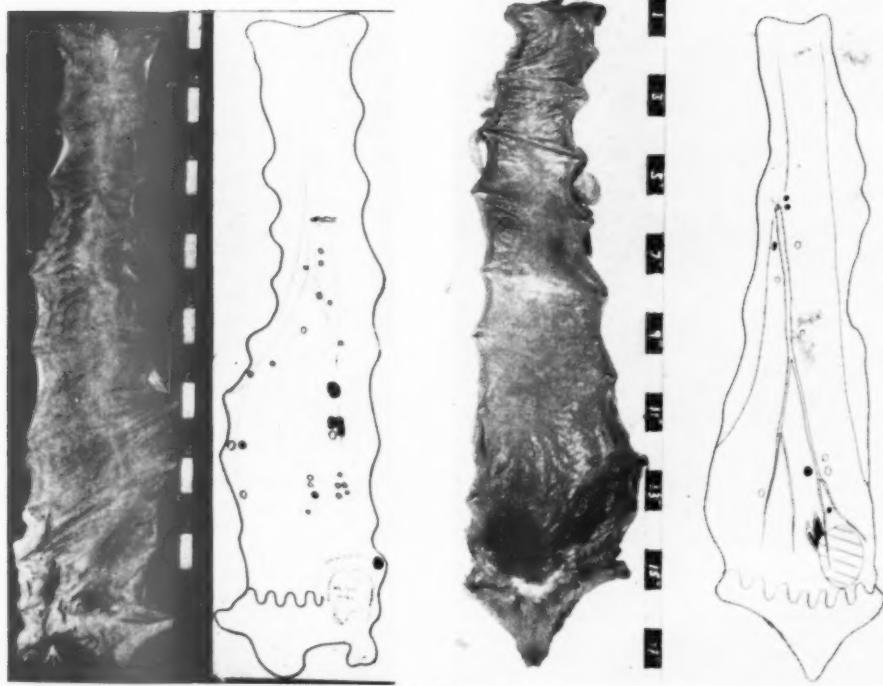
A

C

B

FIG. 10.

D



often by interrupted spread, a combined excision is clearly the best treatment when the primary growth is judged to be operable, but in poor-risk cases a colostomy and perineal excision has still a field of usefulness and may give equally good results. In women if the growth is anterior it is essential to remove the posterior half of the vaginal wall in continuity and not attempt to define a plane of cleavage.

The crude five-year survival rate after excision of the rectum for the period 1941-54 was 51% (29 out of 56 cases). In the differentiated carcinomas of the anal canal the five-year survival rate was 73% (11 out of 15 cases) and in the anaplastic carcinomas it was reduced to 44% (18 out of 41 cases).

Carcinoma of the anus.—There may be differences of opinion as to the best treatment for these cases and some of us will recall the good results obtained by Sir Charles Gordon-Watson by interstitial radium needling. In view of the risk of a radium proctitis developing I think diathermy excision is preferable. A one-quarter-inch margin should be taken on each side and the actual edge of the lesion should not be touched by toothed dissecting forceps for fear of causing implantation of cancer cells. Some of the sphincter muscle can be excised on the deep aspect, and a Δ of tissue should be removed with the apex leading up into the anal canal (Fig. 11). If a haemorrhoid

presents on the side of the lesion it should be ligated and excised or it may subsequently prolapse into the wound in a troublesome way. After removal of the specimen the resulting wound is lightly coagulated with diathermy and is dressed with tulle gras and Milton or Bradosol lotion. The wound is subsequently managed as for a fistula wound with routine irrigations and dressings.

Of 28 cases submitted to surgical treatment between 1941 and 1954 there have been 17 five-year survivors (60%). All but one were treated by local excision and it seems to make little difference whether the histological grade is differentiated or anaplastic. One of the worst cases I can recall was a differentiated squamous carcinoma of the anus in a woman aged 53. The growth was situated in the left posterior quadrant and at the time of operation there was no evidence of unusual subcutaneous spread. After local excision with diathermy a rapid extension took place to the left groin and in spite of a block dissection the growth recurred both in the anal region and in the groin and the patient died within a year of operation.

Metastases to the groin.—Each case must be treated on its merits. I do not believe in routine block dissections of the groin and the operation should only be done if a hard localized enlargement takes place on one or other side according to the site of the primary lesion. I submit that it

is a bad practice to remove a solitary gland for biopsy; if there is a suspicion of inguinal metastases having formed a block dissection should be done. The pathologist should be asked to report on the number of lymph nodes present and the number occupied by metastases: if only one or two contain metastases the prognosis is often good and no further extension takes place subsequently. It would seem that if one gland acts as a filter and enlarges perhaps to a diameter of $\frac{1}{2}$ - $\frac{3}{4}$ in. the prognosis is good provided the block dissection is done while the gland is still mobile and its capsule intact. The prognosis is extremely bad if a chain of 3 or more glands is proved to contain metastases and I do not know of any patients who did not develop recur-



FIG. 11.—Differentiated squamous carcinoma of the anus before and after local excision with cutting diathermy (male, aged 60, July 1950). He remained free from recurrence for seven years when he emigrated to Australia and has not been traced since then. There was no indication at any time for a block dissection of either groin.

rence when a bilateral block dissection of the groins was positive.

I must emphasize the need for regular supervision of the groins after the primary operation whether it is for a carcinoma of the anal canal or the anus. The patient should be seen every month for the first six months after operation and then at two-monthly intervals for at least three years. Even when the five-year mark is reached the patient should not be dismissed and I should like to relate the details of the following remarkable case:

Case I.—Mrs. E. M., aged 65, presented a deeply ulcerated growth involving the anterior wall of the anal canal. Biopsy: squamous cell carcinoma. 29.1.42: left iliac colostomy; 19.2.42: perineal excision. The growth was a flat ulcerating one, $1\frac{1}{2}$ in. in diameter and was an anaplastic squamous cell carcinoma spreading into the sphincter musculature. Six glands were free from metastases—B case. She made a good recovery and remained under regular supervision for ten years and no need arose for a gland dissection of the groins. In June 1952 a gynaecologist performed a vaginal hysterectomy and perineal repair. In March 1954 I repaired a sacral hernia from which she made a good recovery and there was no clinical evidence of recurrence. In July 1954 she was seen and was well. In November 1954 she returned after an interval of four months as instructed, and was found to have developed a hard mobile gland in the left groin. A block dissection of the left groin was done in December 1954 and the one large gland out of 4 examined was proved to contain anaplastic squamous cell carcinoma similar to the primary removed in 1942. This was nearly thirteen years after the original operation. Since then the patient has kept well with no evidence of recurrence to November 1959.

X-ray Therapy

At present X-ray therapy cannot be offered as an equal alternative to radical surgery in carcinoma of the anal canal, chiefly on account of the frequency with which the sphincter muscles are invaded by growth and the liability to early upward lymphatic spread along the superior haemorrhoidal chain.

My impression is that patients with squamous carcinoma of the anal canal who are sent for deep X-ray therapy and fail to respond to treatment or recur after an initial regression of the growth usually do badly when referred back for radical operation. I have notes of 3 cases and only one patient survived for over five years: this was a female aged 54 who has lived for twelve years after colostomy and perineal excision of the rectum after X-ray therapy had failed; the other 2 patients developed early recurrence. In addition one patient with carcinoma of the anus who did not respond to X-ray therapy died of the disease in the same year after perineal excision.

I should like to record the following successful cases of inoperable squamous carcinoma of the anal canal after million volt therapy and this gives me the opportunity of recording the thanks we at St. Mark's Hospital owe to Mr. Ralph Phillips and to Mr. I. G. Williams at St. Bartholomew's Hospital for the invaluable help we have received from their department with many of our cases.

Case II.—A. I., male, aged 68 in May 1942. He presented a deeply ulcerated growth in the lower third of the rectum and anal canal anteriorly and laterally. He had hard enlarged glands in both groins, the right larger than the left. Biopsy showed it to be of the anaplastic basal cell type. A palliative left iliac loop colostomy was done on May 21, 1942. Two weeks later bilateral perianal abscesses anteriorly had to be drained. When these had cleared he was referred to St. Bartholomew's Hospital for X-ray therapy. Three months later the ulcer in the anal canal was small and by February 1943 the anal canal was smooth with no evidence of growth. In January 1944 I closed his colostomy and he was subsequently seen at intervals to August 1951, when his anal canal was normal and the groins clear. He finally died in October 1952 at the age of 78 from cardiac failure, hypertension and arteriosclerosis, i.e. ten years after the course of X-ray treatment.

Case III.—L. A., a Cypriot, aged 48, was referred to St. Mark's Hospital in November 1953 with an advanced carcinoma of the anal canal for which a left iliac loop colostomy had already been performed. The growth was deeply ulcerated anteriorly and of doubtful operability. Biopsy proved it to be anaplastic squamous. I attempted a perineal excision but it was quickly apparent that the growth was quite inoperable and the operation was terminated by cutting the rectum across through the growth below the peritoneal reflexion, chiefly in the hope that removal of the invaded sphincter apparatus would spare the patient subsequent pain to some extent. He was then referred to St. Bartholomew's Hospital for X-ray therapy to which he made a rapid response and when last seen in mid-February 1954 before his return to Cyprus he was excellent. Subsequent enquiry has established that he is still alive and well (March 1960).

These 2 cases suggest, as might be expected, that the high grade anaplastic variety of anal canal growth is the more likely to respond to deep X-ray therapy.

Acknowledgments.—I should like to thank my colleagues at St. Mark's Hospital for allowing me to examine their records when I began this investigation about five years ago and particularly Dr. Cuthbert Dukes for the time and trouble he took when we were reviewing the histology of this series.

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Mr. T. McW. Millar (Edinburgh):

My personal experience of carcinoma of the anus and anal canal is small. Only 2-3 cases of this serious disease are admitted to the 250-300 surgical beds in the Royal Infirmary, Edinburgh, each year. By the courtesy of my surgical colleagues I have been able to review the records of 22 cases admitted during the last ten to twelve years. Though these cases are not complete I have extracted what information I could, and I offer some observations based on that information, on my study of the literature and on my experience.

I found the sex incidence rather more than 2 to 1 in favour of the male sex. The age of the patients varied from 30-83 years, with an average about 60. I found it difficult from case notes to decide in many cases whether the tumour had begun as an anal tumour and had invaded the anal canal or whether it had begun primarily in the latter, but after deciding in each case what I thought had been the primary site I found the number beginning in each site approximately equal.

Inguinal lymph node involvement had occurred in 5 cases, approximately one-quarter. Figures from the literature vary from 8%—30%. Stearns (1955), reviewing 69 cases, found 23% had involvement when first seen and a further 19% developed metastases later.

While a pathological report was available for all cases studied, no grading of the tumours on a histological basis had been done. Various descriptions were used by the pathologists: well-differentiated, 6 cases; well-differentiated but "actively growing" or "with many mitoses", 4 cases; moderately differentiated, 5 cases; poorly differentiated, 4 cases; basi-squamous, 3 cases. There is thus a widespread and an almost equal proportion of the total to each of the main types. I was unable to find any definite correlation between the histological type and the subsequent fate of the patient, except perhaps that undifferentiated tumours of the anal canal carry a bad prognosis. I think Wittoesch *et al.* (1957) refer to the same tumour as basaloid small cell carcinoma, which, they find, occurs near the dentate line, is highly malignant and gives poor results after treatment.

Treatment employed in this series has been on the usual lines. About three-quarters were treated surgically and the remainder by surgery and radiotherapy, or by radiotherapy alone, usually as a palliative measure.

Of the 22 patients studied 3 survived for at least eight, five, and four years. 9 are dead or presumed dead because it was known that the disease was not controlled. In 2 cases there is no record of the patient having reported to hos-

pital after the primary treatment. Of the remaining 8, 3 are recent and the other 5 were known to be alive and well for periods round about one year after treatment when follow up ceased.

Lymphatic Spread

This disease presents several problems, not the least of which is how to deal with the regional lymph nodes, whether these are involved clinically or whether they are apparently uninvolved. It is generally agreed that tumours of the anus metastasize to the superficial inguinal nodes via lymphatics which pass forward between the perineum and the upper medial thigh. The further spread is along the external and common iliac vessels to the pre-aortic nodes, but I would call attention to the possibility of involvement of what are called the obturator nodes which lie over the entrance to the obturator canal and which apparently can become involved by spread from the inguinal nodes even in the absence of involvement of nodes along the iliac vessels. Several authors refer to this involvement, and I have seen these nodes heavily invaded by carcinoma in a patient who had massive involvement of the inguinal group but no involvement of the iliac group. These obturator nodes lay proximal to the point at which the obturator artery and nerve entered the obturator canal and were lightly adherent to these structures.

When the tumour originates in the anal canal the lymphatic drainage is both more complicated and more difficult to deal with surgically. There may be a spread upwards with involvement of the pararectal, superior rectal and inferior mesenteric nodes. Such a spread is satisfactorily dealt with by the abdominoperineal operation. The lateral spread along the inferior rectal (haemorrhoidal) and middle rectal vessels leads to involvement of nodes along the levator muscles and the internal iliac nodes on the side wall of the pelvis. These nodes are not dealt with in the classical abdominoperineal operation and a deep pelvic node dissection has been suggested and practised in an attempt to deal with them. I cannot say much about this from personal experience but I have, on occasion, attempted such a dissection when operating for a low carcinoma of the rectum in which I thought there was evidence of lateral spread and I found the procedure difficult and unsatisfactory.

Treatment of the Primary Lesion

It is generally agreed that small superficial lesions of the anus, involving only a sector of the circumference (perhaps not more than a third) and not extending far up the anal canal should be treated by wide local diathermy excision, even if some of the outer layers of the external sphincter

muscle have to be sacrificed. The resulting wound may be covered with an immediate skin graft. For larger anal lesions, and for all tumours originating in or extensively involving the anal canal the abdominoperineal excision is the correct treatment. In carrying out the perineal part of the operation wide removal of the ischiorectal fat and levator muscles should be performed. Whether such an excision should be combined with an attempt at deep pelvic node dissection is a moot point.

Treatment of the Lymph Nodes

With regard to the treatment of the inguinal and iliac lymph nodes I would agree that, if one is satisfied on clinical examination there is no suspicion of inguinal involvement, no removal of these nodes should be carried out. I do not favour prophylactic groin dissection.

I would, however, emphasize strongly the necessity for careful post-operative review of patients who have had the primary lesion dealt with by one means or another, but who have not had groin dissection carried out. Recurrence in the inguinal nodes may appear early or late, and I have been impressed with the rapidity with which such a recurrence may grow. An elderly patient, who had had a local removal of the tumour, had no clinical evidence of inguinal involvement before operation nor up to three months after operation, at which time he defaulted. Five months later he had an almost inoperable mass in one groin.

Operation for groin metastases at an early stage, with perhaps only one node palpably enlarged, is well worth while, and by careful follow up after treatment of the primary such metastases should be found at an early stage. I have referred to the review by Stearns (1955) of 69 cases of epidermoid carcinoma in the anal region in which he found inguinal metastases in 29: in 16 cases the nodes were obviously involved at the first admission, and in 13 they appeared subsequently, nearly all within two years; 9 of the 16 were submitted to groin dissection and 8 of the 13 follow-up cases were operated on—a total of 17. All those with involved nodes when first seen had died, but 5 of the 8 whose metastases were discovered on follow-up examination were well from two to six years later. Careful follow up and operation as soon as inguinal involvement is discovered may be rewarding.

Our practice in dealing with regional lymph nodes in the groin has not been quite logical and not in line with our practice elsewhere, e.g. the radical dissection of the axilla or the block dissection of the neck where we do not hesitate to do an extensive operation with wide removal of the deep fascia, the sternomastoid muscle and the

internal jugular vein. The reason for this is not far to seek. Lee (1955) has described removal of the inguinal lymph nodes in the past as a bugbear, vexatious to the surgeon and a sore affliction to the patient. As commonly performed it carries a considerable morbidity from necrosis of the skin flaps with delayed healing by granulation, lymph fistula, infection and consequent oedema of the limb. Furthermore a true ilio-inguinal block dissection cannot be done if it is agreed that the inguinal ligament should not be divided. But can most of these difficulties not be overcome? I would agree that a superficial inguinal node dissection might be considered adequate for early involvement, but if we are going to operate at all for more serious involvement surely we should carry out the most radical operation possible. In this connexion I would draw attention to the ilio-inguinal block dissection described by Lee (1955). By this method a truly radical operation is done, primary healing of the wound can be obtained without drainage and without the leakage of lymph, and, in my own experience, lymphoedema of the leg is not marked and occurs chiefly in the thigh.

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Mr. W. H. Bond (Birmingham):

True squamous cell carcinoma of the anus is rare; between 1936 and 1956 the United Birmingham Hospitals registered only ninety-six cases—about 0.1% of all malignancy. To provide five-year figures the initial study was done on the 73 cases treated up to 1954, but in common with squamous cancer at most other sites, three-year figures give determinate results, for only one death from growth occurred between the third and the fifth year. Histological proof was not obtained in all, but all tumours in which the rectum was involved were proven as were all but two of those treated in an attempt to cure (Table I).

		3-year survivors
1936-1954	Palliative or no treatment—	24 0%
	Radical surgery or radiation—	49 36.7%
1936-1956	Palliative or no treatment—	34 0%
	Radical surgery or radiation—	62 38.8%
	Histological proof 73 cases	
	Overall five-year survival rate 1936-1954—24.6%	

The classification adopted depends on the anatomical extent of the tumour and its site. Anal: In this group the tumour lay mainly

externally. Anal canal: Here, though the skin may have been involved, the greater extent lay in the canal. Anorectal: The tumour arose in the upper part of the anal canal and extended within the internal sphincter to involve the rectum.

The age incidence (Table II) and symptom-

TABLE II.—AGE INCIDENCE (1936-1954)

	Age in years										
	40	45	50	55	60	65	70	75	80	85	
Anus	M	14	4	—	1	2	2	3	3	4	—
Anal canal	M	31	4	—	3	3	4	5	8	7	5
Anorectal	M	9	11	3	1	2	1	3	2	5	1
Total		3	5	7	7	11	13	15	9	1	2

tology did not differ in the three groups, save that the 3 youngest and the 3 oldest were all anorectal tumours; the maximum incidence was between 60 and 70. There are differences in the sex incidence for whereas 55% of the anorectal series are female, this sex is affected in only 15% of the anal and anal canal series. Inguinal node involvement when first seen is similar in all groups, no case surviving into a third year (Table III). 6 cases developed nodes after an

TABLE III

	Percentage presenting with clinical node involvement	Percentage treated palliatively or not treated
Anus	28%	3/18 17%
Anal canal	34%	11/35 31%
Anorectal	30%	10/20 50%
All cases	30%	24/73 31%

attempt at radical treatment, in spite of radiation or lymphadenectomy and died before the third anniversary. In common with malignancy at other sites distal metastasis was commoner in those with nodes at any stage, and I have little support for attempts at curing those with involved inguinal nodes. This is a sad conclusion for 10% of the deaths are attributable to catastrophic haemorrhage from an eroded femoral artery.

Treatment of the primary tumour.—There were 24 patients for whom no curative procedure was undertaken. Half died within six months of first attendance and all died within two years.

By modern standards undoubtedly perineal or abdominoperineal excision would be done in some and there is a definite place for a short course of X-ray therapy to simplify nursing care. 49 cases received curative treatment, 28 by radiation and 21 by surgery, successful in 18, giving a five-year cure rate of 36.7%, the overall rate being 24.6%.

The tumours treated by radical radiation (Table IV) were nearly all anal or anal canal,

TABLE IV.—CASES TREATED BY RADICAL RADIATION METHODS (1936-1954)

Anus	10	28
Anal canal	16	
Anorectal	2	
Primary site healed	12	(43%)
Uncontrolled tumour	5	
Local recurrence	4	16 (57%)
Radiation necrosis	7	
Spread to inguinal nodes	3	
Distal metastases	2	
Average age	65 years	
Five-year survivors	9 (32%)	

only 2 being anorectal. Local control of disease during the lifetime of the patient was obtained in 12, 16 failed from recurrence, radioresistance or necrosis. The average age was 65 and the five-year survival rate 32%.

The techniques of radium implant require no special description, planar implants being used for the smaller lesions, a volume implant with or without a central source in the canal for the larger. Radium needle implant is technically difficult and commonly geometrically unsatisfactory; even so, the study of dose levels is useful. Overdosage not only gives a high incidence of radiation damage, but local recurrence and failure to control the tumour increase in frequency. This possibly arises from a biological effect, but errors in the needle implant are merely magnified by the higher dosages. In this series local complications arose in 13 of 16 given 6,000 r or over, but in only 3 of the 11 treated to lower dose levels (Table V). A fair

TABLE V.—CASES TREATED BY RADICAL RADIUM IMPLANT (1936-1956)

	4,500 r and under	5,000 to 5,500 r	6,000 r and over
Primary site healed	3	8	3
Uncontrolled tumour	0	1	4
Local recurrence	0	0	13/16
Radiation necrosis	0	2	5
Spread to inguinal nodes	1	1	1
Distal metastases	0	4	1
Total	3	11	16
Three-year survivors	2	5	6 (43%)

conclusion is that the dose level at 0.5 cm from the radium should not exceed 5,500 r in five to seven days, and the use of simpler and more controllable implants to a lower dosage level in recent years may account for the 43% three-year survival rate when the more recently treated cases are included.

The picture presented by the 21 cases treated surgically (Table VI) is happier, local control

TABLE VI.—CASES TREATED BY RADICAL SURGICAL METHODS (1936-1954)

Anus	5	21
Anal canal	8	
Anorectal	8	
Primary site healed	13	(61%)
Uncontrolled tumour	1	
Local recurrence	6	7 (33%)
Spread to inguinal nodes	3	
Distal metastases	5	
Average age	58 years	
Five-year survivors	9 (43%)	

being obtained in 13; only 7 had persistent or recurrent disease. There was one post-operative death. The average age was somewhat lower at 58, and the three- and five-year survival rate 43%. In the whole series of 27 (Table VII), 9 were

TABLE VII.—CASES TREATED BY RADICAL SURGICAL METHODS (1936-1956)

	Local excision	Perineal excision	Total
Primary site healed	4	12	16
Uncontrolled	1	—	1
Local recurrence	2	5	7
Spread to inguinal nodes	1	3	4
Distal metastases	2	5	7
Total	9	18	27
Three-year survivors	4	9	13 (48%)

treated by local excision, three recurred locally and 4 survived three years. The result of the 18 perineal or abdominoperineal excisions was better, with a 50% three-year survival rate, only 5 in 18 recurring locally.

These results may be due to selection, save that some surgeons consistently excised the tumours and others always referred them for radiation. On this basis one may presume fairly random selection, although the difference in average ages suggests that this is not the case.

In presenting the case for radiotherapy I know that the figures given show a slight bias in favour of surgery, preferably radical as opposed to local excision. Consideration shows that at modest dosage levels the local cure by radiation is as good as that achieved by surgery, and only in the incidence of necrosis does radiation fall behind, distal metastases and node recurrence being equally common with either method. In the larger tumours and those extending into the rectum surgery offers greater benefit, but successful surgery depends on the patient's willingness to sacrifice the anus, and one-third of the patients are over 65, when major surgery for a seemingly minor lesion may be undesirable.

Any treatment scheme for anal carcinoma must include radiation, as a palliative for the incurable and as a method of choice for selected cases.

In *anorectal* lesions external methods of radiation and radium needling have little part to play. Whilst a tumour lying mainly on the anterior wall of the rectum can be implanted, posterior and laterally sited lesions above the internal sphincter cannot be adequately covered by needle implant. Fig. 1 illustrates the difficulty, for the tumour lies on the double curve at the junction of rectum and anal canal, and it is virtually impossible to design an implant which fully treats the tumour and avoids necrosis. A possible solution is the use of radioactive gold grains, but this group are unquestionably best treated by abdominoperineal excision. Tumours of the *anal canal* may be treated by a curved single plane implant using 42 mm or 58 mm needles, and with care a parallel implant can be achieved (Fig. 2). It has, however, one weakness in that it is impossible to close the top of the implant by a crossing needle, and this considerably reduces the fully treated area. Even using differentially loaded needles this objection remains and recurrence appears from under-dosage. A possible solution is a gold grain implant, for the tissues can be drawn over the needle, the additional top loading provided by two or three grains placed in one spot, the rest of the chain inserted as the needle is withdrawn. The pattern of a radium needle implant can be readily reproduced, with the additional advantages that no needles have to be removed, neither will they slip out of place, and finally nursing is easier for bowel movements take place normally.

Somewhat similar considerations apply to tumours of the *anus*. These tumours can be effectively treated by a single plane radium im-

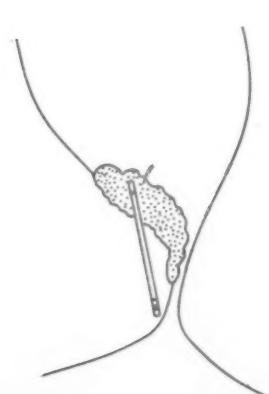


FIG. 1.



FIG. 2.

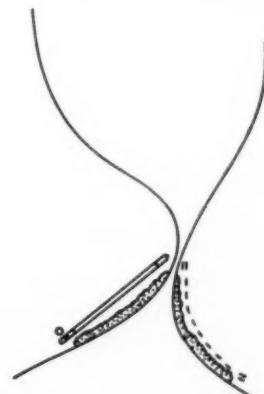


FIG. 3.

plant, but as with anorectal tumours one has to deal with a double curve at the junction of the anus and canal (Fig. 3). Here, since these tumours are fairly superficial, one can deal with the problem by threading the needle just deep to the skin so that the curves are obliterated. This distortion of the tissues, however, stretches the external sphincter which on contracting distorts the implant and extrudes the needles. Again this implant is weak at the uncrossed end, and the solution is probably a gold grain implant which, accurately performed, avoids the difficulties of a rigid radium needle insertion.

Selection of cases.—All anorectal tumours are best treated surgically; failing this, gold grain implant has much to commend it for full dosage can be given in safety to the whole of the tumour. Lesions of the anus and anal canal involving less than half the circumference, of superficial character and less than 1.0 cm thick are fully treatable by radiation. The smallest are best excised for healing is quicker than after implant, and the larger, where the growth is still local, should be removed by abdominoperineal excision.

Mr. Gordon S. Ramsay (London):

Treatment

I have based my remarks, mainly, upon an analysis of cases seen at the Royal Marsden Hospital from 1940 to 1959, and at the Gordon Hospital from 1947 to 1959.

I excluded 5 cases that were recorded as having squamous cell carcinoma of the anus, but in whom the diagnosis was either wrong or doubtful. One was a large papillomatous lesion of the buttock which was histologically benign and which was cured by local excision. Two were straightforward basal cell tumours which require no comment and the remaining 2 patients each had anaplastic growths. The first was in a woman of 81; it extended 5 cm up the anal canal and also involved the perianal skin and was so anaplastic that it was impossible to determine its aetiology; she died nine months after treatment with high voltage therapy (H.V.T.) and radium needles, having developed metastases in the buttock and groin. The second was diagnosed originally as being a double primary, adeno and squamous, but on review belongs to the rare group of muco-epidermoid tumours arising from the ducts of the anal glands—it certainly bears no resemblance to either squamous or adenocarcinoma.

There remain 50 cases for study, 28 men and 22 women. Their age and sex distribution is shown in Fig. 1 which emphasizes the fact that this disease usually affects elderly people. The division of the cases into three grades of malignancy (Table I) using the criteria of Mr. Gabriel (1941),

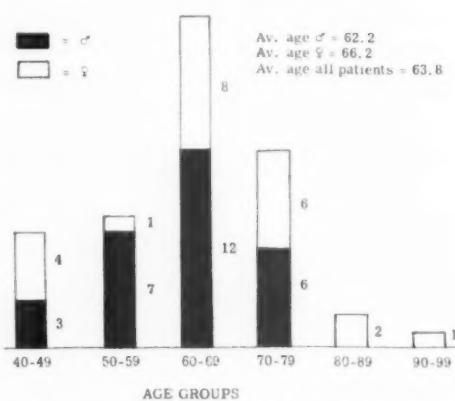


FIG. 1.—Squamous cell carcinoma of anus, Royal Marsden and Gordon Hospitals series. Age and sex on entry (50 patients).

illustrates the tendency for low-grade tumours to occur more commonly in men and for high-grade tumours to affect women. The 6 cases not graded had had biopsies taken at other hospitals and, although there is no doubt about the diagnosis, the reports made no mention of the degree of differentiation of the tumour and I have been unable to obtain the slides for review. The site of origin is also different in the two sexes; of 22 patients with anal canal tumours 10 were male and 12 female, whilst of the 28 patients with anal margin tumours, 18 were male and only 10 female.

TABLE I.—SQUAMOUS CELL CARCINOMA OF ANUS
50 CASES GRADED HISTOLOGICALLY

	Males	Females	Total
Low grade	9	5	14
Medium grade	9	3	12
High grade	8	10	18
Not graded	2	4	6
Total	28	22	50

It is extraordinary how advanced many of the cases are when they reach hospital and simple clinical staging based upon the size of the growth (up to 3 cm—early, more than 3 cm—late) shows that almost two-thirds of this series were late cases (Table II).

41 cases are available for assessment of five-year survival (Table III). (I have avoided the use of percentages in this small series.)

The fate of the patients in the various groups was as follows: Of the 14 patients with well-differentiated growths, 6 are alive for periods of from three to nine years and 3 others died from unrelated causes: 1 in the fourteenth year, cause unknown, 1 in the fifth year from carcinoma of the bronchus and 1 from peritonitis twelve days after an abdominoperineal (A.P.) excision of the rectum. The remaining 5 patients all died from recurrence of their disease in less than two years.

TABLE II.—SQUAMOUS CELL CARCINOMA OF ANUS
CLINICAL STAGING AND HISTOLOGICAL GRADE

	Early	Late	Total
Low grade	8	6	14
Medium grade	4	8	12
High grade	6	12	18
Not graded	1	5	6
Total	19	31	50

TABLE III.—SQUAMOUS CELL CARCINOMA OF ANUS
FIVE-YEAR SURVIVAL

	All cases	Five-year survivors
Low grade	13	6
Medium grade	7	3
High grade	15	2
Not graded	6	1
Total	41	12

All 6 patients with early anal margin lesions were cured by local excision. One patient with an early anal canal growth is alive three years without recurrence after an A.P. excision. The other patient who had an A.P. died from peritonitis and one died from recurrence after perineal resection. The remaining 5 were treated with radiotherapy; 3 had a preliminary colostomy. 4 received high voltage therapy and the only success was achieved in the fifth patient, a man of 63. His primary was treated with about 5,000 r at 60 kV in sixteen days and both inguinal regions were then treated with H.V.T. He died four years eleven months later from carcinoma of bronchus.

Of the 12 medium-grade cases, 7 are alive. 1 was treated only 4 months ago and the remaining 6 survived from three to six years; 2 died without recurrence, 1 in the ninth year from pneumonia and 1 in the fifth year from coronary thrombosis.

Of the 6 who survive more than three years, 3 had A.P. excisions, 2 had local excisions and one, a woman of 68, received 2,900 r skin dose in twenty-three days at 220 kV. Two months later radium needles were implanted and she received a further 5,000 r. She remains well six years after treatment apart from a small area of radio-necrosis which she steadfastly refuses to have excised.

The other 2 successes were treated by surgery. One, an early case, was treated by diathermy excision, and the other, more advanced, had a perineal excision of the rectum.

3 died of their disease, 1 from recurrence following perineal excision of the rectum, another, advanced, was untreated and the third was a woman of 75 with a late anal canal growth which was treated by a combination of H.V.T., low voltage therapy and the interstitial implant of radioactive gold grains. The tumour failed to respond and a palliative abdominoperineal excision of the rectum was carried out. At operation, extensive spread in the pelvis was found and post-mortem examination shortly afterwards

revealed multiple metastases in the lungs and in the bladder.

The high-grade group of 18 patients presents a gloomy picture. Only 3 survive, all treated by abdominoperineal excision of the rectum and are free from recurrence ten, nine and three years after operation.

The remainder died of their disease with the exception of one patient who succumbed to a pulmonary embolus fifteen days after A.P. excision of the rectum but at autopsy was found to have multiple metastases in the liver and pelvic lymph nodes.

3 were early cases and were treated by local excision and all recurred rapidly. The remaining 12, all late cases, were treated as follows: 6 had radical surgery and 6 radiotherapy. The longest survival was two years ten months.

The ungraded group is also depressing. 1 man is alive nine years nine months after radium needle implant. 1 woman aged 65 received approx. 6,000 r at 60 kV to the anus in twelve days. She developed marked stenosis, but when she died three years later from cardiac failure there was no sign of recurrence. The remaining 4 patients died of their disease. 1, a man aged 77 with advanced disease and poor general condition, was not treated and the rest, all women with late anal canal lesions, were treated with radiotherapy with no success.

The treatment of carcinoma of the anus is still controversial and it is impossible to lay down hard and fast rules for every case, but there are a few lessons to be learned even from this small series.

During the past twenty years there has been a tendency to use surgery in preference to radiotherapy in the treatment of the operable case. This change has occurred because of the disappointing results of radiotherapy; the unpredictable response of the primary, the necessity for a colostomy in some cases and the frequent production of pain and tenesmus. It is now generally agreed that radiotherapy is incapable of controlling lymph-node metastases in most cases. In this series there were 4 successes from radiotherapy alone, but in a further 9 patients, in whom there appeared to be some hope of cure, it failed. Surgery appears to offer a little more hope; it may be local or radical (as in this series), or super-radical as advocated by some American surgeons. Local surgery should be reserved for really small lesions at the anal margin, proved by biopsy to be of low-grade malignancy, and all other operable cases should be treated by abdominoperineal excision of the rectum. There is not enough evidence yet to show whether or not radical abdominopelvic and inguinal node dissections are of value, but it is interesting to note that, of 12

patients who had an A.P. excision and in whom the pararectal lymph nodes were found to be tumour free, 4 died from local recurrences and another, who died of a pulmonary embolus, was found to have involvement of the pelvic nodes although the pararectal nodes were free. It is in the treatment of such cases as these that the super-radical operation may have a place.

Management of the inguinal nodes.—Few patients who develop inguinal node metastases live five years. In this series there is one man who has no sign of recurrence four years ten months after an A.P. excision followed six months later by a right inguinal block dissection; both the pararectal and the inguinal nodes were involved. Inguinal node dissections were done in 11 other cases, in 7 the nodes were involved and these patients died in less than six months, in the remaining 4 cases the nodes showed evidence of chronic inflammation only. Stearns (1955) has demonstrated convincingly the futility of doing prophylactic inguinal node dissections and, since the operation is one associated with considerable morbidity, it should, in my opinion, be reserved for use if and when the nodes become involved. The difficulty is in deciding when this is so as clinical judgment is often wrong. There were no prophylactic dissections in this series and the 4 patients whose nodes were found on histological examination to be unaffected suffered an unnecessary operation. This error could be avoided by the use of the frozen section technique, one of the most satisfactory applications of which is the detection of squamous cell carcinoma in lymph nodes, and I advocate strongly its use in this type of case.

The plan of treatment may be summarized as follows: (1) Biopsy in all cases, however small the lesion. (2) Local excision reserved for lesions that are small, at the anal margin and of low-grade malignancy. (3) All other operable cases to be treated by abdominoperineal excision of the rectum. (4) Inguinal nodes should be observed and if suspicious, frozen section followed by block dissection if section is positive. (5) Radiotherapy as palliative treatment in the advanced case.

Acknowledgments.—I wish to thank the surgical staffs of the Royal Marsden and Gordon Hospitals for permission to use the case records. I am grateful to Dr. I. P. M. Dawson and Dr. N. F. C. Gowing for reviewing some of the histology.

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Dr. Basil C. Morson (London):

The Pathology and Results of Treatment of Squamous Cell Carcinoma of the Anal Canal and Anal Margin

In his Presidential Address to the Section of Proctology of this Society Mr. W. B. Gabriel (1941) emphasized the differences between squamous cell carcinoma of the anal canal and squamous cell carcinoma of the anal margin. I shall describe the differences in the pathology of these anal cancers together with some comments on their diagnosis, treatment and prognosis from the point of view of a pathologist.

It is necessary first to attempt an anatomical definition of what we mean by anal canal carcinoma and anal margin carcinoma. At St. Mark's Hospital we have chosen to classify all anal cancers by their relationship to the dentate line or line of the anal valves, as judged by the examination of operation specimens or, in the absence of such a specimen, by reference to the clinical notes (Table I). The

TABLE I.—POSITION OF PRIMARY TUMOUR IN 157 CASES

Anal Canal:		
Entirely above the dentate line . . .	38	85
Mainly above the dentate line . . .	47	
Exactly astride the dentate line . . .	18	
Anal Margin:		
Mainly below the dentate line . . .	13	38
Entirely below the dentate line . . .	25	
Unclassified . . .	16	
		157

position of the primary tumour in 157 cases of squamous cell carcinoma of the anal region seen at St. Mark's Hospital from 1928 to 1956 has been so defined. All squamous cell cancers lying entirely above, mainly above or exactly astride the line of the anal valves have been defined as anal canal tumours, whereas those lying mainly below or entirely below the line of the anal valves are regarded as anal margin tumours. This is an arbitrary classification, but in practice it works well from both the clinical and pathological points of view.

By the above criteria it has been possible to classify all but 16 of these 157 tumours. Either these were large growths or records were inadequate for an accurate estimate of the site of origin. Of the remaining 141 cases, 103 were anal canal tumours and 38 anal margin tumours. Thus anal canal cancer is about two and a half times as common as anal margin cancer. However, it is of interest that of the 103 anal canal cancers 85 arose above or mainly above the line of the anal valves and 38 of these lay entirely above this line. It is not sufficiently known that such a high proportion of squamous cell carcinomas of the anal canal arise from epithelium entirely above the line of the anal valves (Fig. 1).

The normal epithelial lining of the anal cana



FIG. 1.—Squamous cell carcinoma of anal canal. The tumour is arising from epithelium entirely above the level of the anal valves.

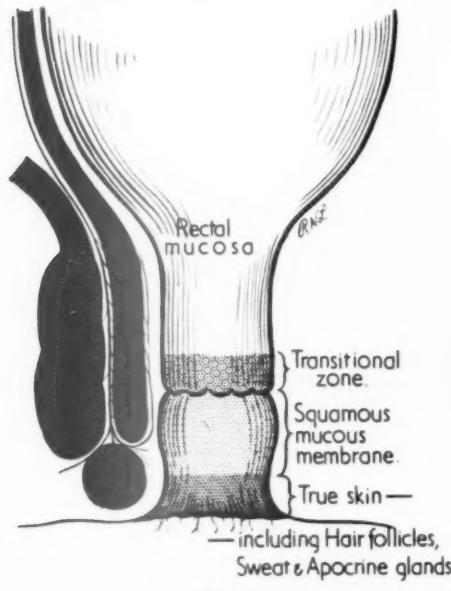


FIG. 2.

and perianal region is illustrated in Fig. 2. The anal canal above the anal valves is lined by rectal mucosa except for a narrow zone, seldom more than half an inch wide, immediately above the valves and covering the lower part of the internal haemorrhoidal plexus, which may be called the "transitional" or "junctional" zone, as the structure of its epithelium is a compromise between the glandular rectal mucosa above and the squamous mucous membrane or modified skin below the level of the valves which merges with the true skin of the perianal region. The transitional or junctional zone, as pointed out by Walls (1958), is an area of considerable epithelial instability which contains a number of different varieties of epithelium. Here we may see a transitional type of mucosa (Fig. 3) resembling urinary tract epithelium, stratified columnar epithelium and squamous mucous membrane (Fig. 4) as well as "mixed" epithelium which may show features of all these varieties and also contains scattered

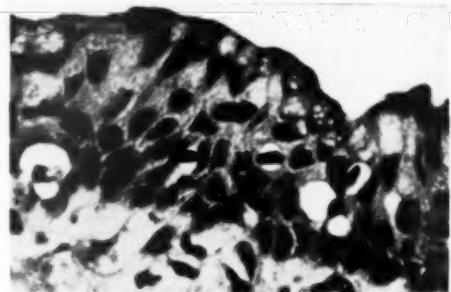


FIG. 3.—Transitional epithelium from the transitional or junctional zone above the line of the anal valves. The appearances resemble urinary tract epithelium but some of the cells in the superficial part of the mucous membrane are secreting mucus and can be seen in the photograph as goblet cells. $\times 400$.

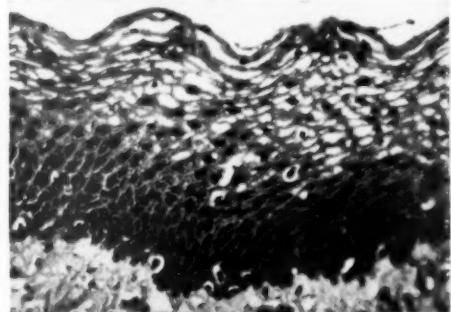


FIG. 4.—Simple squamous epithelium. This is the lining of the anal canal below the level of the anal valves but in many cases is also found in the transitional zone above the valves. $\times 400$.

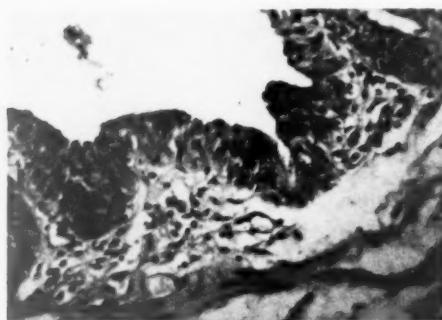


FIG. 5.—"Mixed" epithelium from the transitional zone above the anal valves which is stratified columnar but also contains mucus-secreting goblet cells. $\times 350$.

droplets of mucous secretion (Fig. 5). The structure of the epithelium in this junctional zone varies with age and with pathological changes, such as haemorrhoids.

Most anal canal cancers arise from the unstable transitional zone of epithelium above the anal valves. It is not surprising, therefore, that anal canal carcinomas have a variable histology. Many of them resemble bladder carcinoma, and indeed the diagnosis of transitional cell carcinoma of the anal canal is commonly made by pathologists. The term basal cell carcinoma of the anal canal or basi-squamous carcinoma is also used because of the resemblance of some anal canal cancers to rodent ulcer. However, true rodent ulcer or basal cell carcinoma of the anus is a non-metastasizing tumour of the perianal skin and is rare. The tumours of the anal canal, called "basal cell" by some, are metastasizing tumours and should be treated as for squamous cell carcinoma. To avoid confusion I call all these anal canal cancers "non-keratinizing squamous cell carcinoma", because most of them produce little keratin. On the other hand squamous cell tumours of the anal margin are mostly of the keratinizing type (Table II).

TABLE II.—RELATIONSHIP OF SITE TO KERATIN PRODUCTION IN SQUAMOUS CELL CARCINOMA		
	Proportion of cases forming keratin	
Anal canal	45.1%	
Anal margin	84.2%	

For many years it has been customary to regard keratin production as a rough guide to the degree of malignancy of squamous cell carcinoma. The greater the amount of keratin the lower the grade of malignancy. This is the main reason why the prognosis of anal margin disease after surgical treatment is better than anal canal carcinoma.

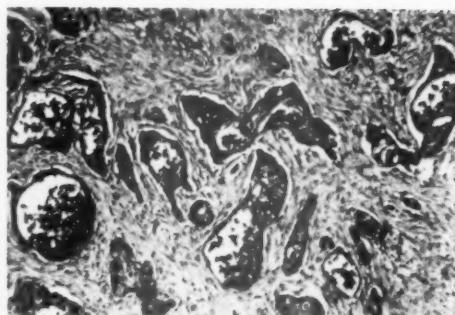


FIG. 6.—Muco-epidermoid carcinoma of anal canal. Typically this arises from the transitional zone and tumours of this type are only found in the upper part of the anal canal. $\times 80$.

The anal canal is one site where muco-epidermoid carcinoma may be found (Fig. 6). This tumour is a type of squamous cell carcinoma which produces mucus as well as differentiating towards keratin production. It is found exclusively above the anal valves, arising from the transitional zone of epithelium, and is a reflection of the epithelial instability of this area. Muco-epidermoid carcinoma is found at other squamo-glandular junctional zones, such as in the cervical canal, but it has no pathological properties which suggest any special form of treatment.

Because of the great histological variability I have not found histological grading of squamous cell carcinoma of the anal canal of much value. If grading is requested a simple distinction between differentiated or keratinizing squamous cell carcinoma and undifferentiated or non-keratinizing squamous cell carcinoma is the best one can do. Such a classification is an approximate guide to prognosis.

Anal margin carcinoma arises from the lower part of the anal canal lined by simple squamous mucous membrane and from the perianal skin. I would go farther and suggest that most anal margin tumours arise from the junction of skin and mucous membrane. This junctional origin, the appearance of the tumour, its histology and behaviour suggest a comparison with carcinoma of the lip. At both sites we are dealing with a keratinizing squamous cell carcinoma, usually of a relatively low grade of malignancy, which is much commoner in males than females and metastasizes to the regional lymph nodes at a late stage in its history.

Age and Sex Incidence (Table III)

The sex incidence of anal canal and anal margin cancer is different. In the St. Mark's cases, anal canal tumours are commoner in women, in a proportion of about 4 : 3, whereas anal margin

TABLE III.—SQUAMOUS CELL CARCINOMA OF ANAL CANAL AND ANAL MARGIN
St. Mark's Hospital, 1928-1956

Sex ratio	Males	Females	Ratio of males to females
Anal canal	44	59	3 : 4
Anal margin	31	7	4.4 : 1
Average age			
Anal canal	57.5 years		
Anal margin	57.9 years		

cancer is about 4 : 1 in favour of men. The age incidence shows no difference between the two sites, or any significant difference when compared with adenocarcinoma of the rectum.

Spread (Figs. 7, 8, 9 and 10; Table IV)

(1) *Direct*.—Squamous cell carcinoma of the anal canal shows preferential direct spread upwards into the lower third of the rectum and this explains why many squamous cell carcinomas of the anal canal present clinically as tumours of the

lower rectum. Direct spread occurs by permeation of malignant cells along lines of least resistance such as tissue spaces and natural anatomical clefts. In anal canal cancer the line of least resistance appears to be upwards in the submucous layer, often with secondary ulceration through the rectal mucosa. Downward spread is held up by the arrangement of the anal musculature and in particular by the mucosal suspensory ligament of Parks, which partly obliterates the submucosal layer at its attachment to the squamous mucous membrane in the region of the anal valves.

(2) *Lymphatic* (Table IV).—Anal canal cancer spreads to the superior haemorrhoidal lymphatic glands, the glands on the lateral walls of the pelvis as well as to the inguinal glands. There is haemorrhoidal gland involvement in 42.9% of



FIG. 7.

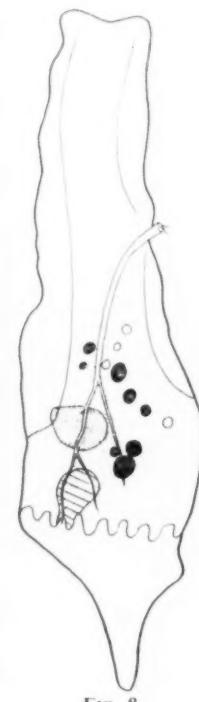


FIG. 8.

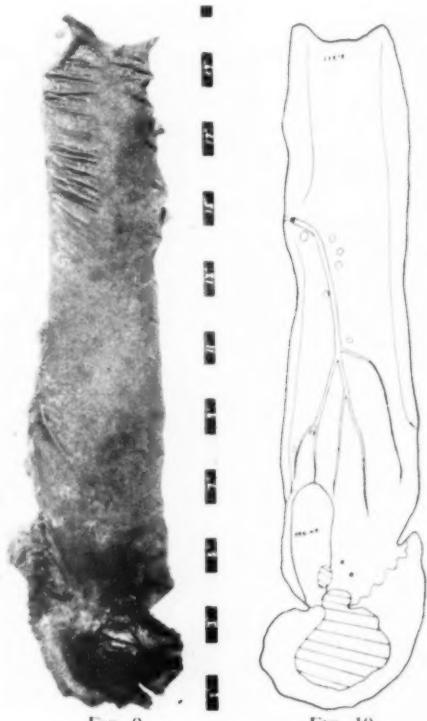


FIG. 9.

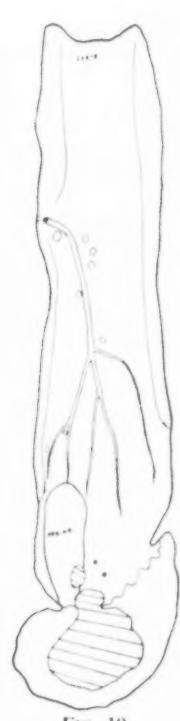


FIG. 10.

Fig. 7.—Squamous cell carcinoma arising from epithelium above the line of the anal valves with preferential spread upwards into the rectum.

Fig. 8.—Line drawing of specimen illustrated in Fig. 7 showing deposits of growth in haemorrhoidal lymphatic glands.

Fig. 9.—Large squamous cell carcinoma of anal margin with involvement of the anal sphincters and early spread into the lower third of the rectum.

Fig. 10.—Line drawing of Fig. 9. There are no lymphatic metastases in the haemorrhoidal glands.

Figs. 1, 7, 8, 9 and 10 are reproduced from Morson (1960) by kind permission.

major operation cases of anal canal cancer seen at St. Mark's Hospital, and clinical and pathological evidence of inguinal gland metastases in 35.9% of cases. However, there is clinical evidence that in anal canal carcinoma the inguinal glands are involved at a later stage than the haemorrhoidal glands.

TABLE IV.—LYMPHATIC SPREAD IN SQUAMOUS CELL CARCINOMA OF ANUS

St. Mark's Hospital, 1928-1956		
Hæmorrhoidal glands (major operation cases only)	42.9%	
Inguinal glands (all cases)	35.0%	
Inguinal glands: Anal canal	35.9%	
Anal margin	39.5%	
Hæmorrhoidal glands involved in anal margin cases treated by excision of rectum	0.0%	

In anal margin disease, inguinal gland metastasis has been found in 39.5% of cases. Most of these patients were treated by local excision of the primary tumour, but of the 9 cases of anal margin cancer which were so extensive as to require a radical operation none showed involvement of the hæmorrhoidal group of lymphatic glands (Figs. 9 and 10). It would appear that hæmorrhoidal gland involvement is extremely rare in anal margin cancer, if it ever occurs, and this justifies the current practice of local excision of these tumours where possible.

Treatment (Table V)

TABLE V.—COMPARISON OF OPERATIVE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL AND ANAL MARGIN

St. Mark's Hospital, 1928-1956		
Treatment	Anal canal	Anal margin
Major excision	79 93.0%	9 31.0%
Local excision	6 7.0%	20 69.0%

There is no significant difference between the operability rates for the two sites, the figures being 85.9% for cancers of the anal canal and 78.4% for those of the anal margin. The method of removing the growth in operable cases, however, differs considerably in the two groups. Whereas only 6 of the 85 anal canal tumours (7.0%) were removed by local excision, no fewer than 69% of the 29 anal margin growths received a limited excision.

Prognosis (Table VI)

The crude five-year survival rate of all 157 cases of squamous cell carcinoma of the anal region seen at St. Mark's Hospital from 1928 to 1956 is 42.6%, which is slightly better than the crude five-year survival of all cases of adenocarcinoma of the rectum. Reports from the United States (Grinnell, 1954; Stearns, 1958) agree that the

TABLE VI.—SURVIVAL RATE OF SQUAMOUS CELL CARCINOMA OF ANUS

St. Mark's Hospital, 1928-1956		Anal canal		Anal margin	
Five-year survival rate: Crude	42.6%	(rectal cancer = 34.7%)	Corrected	50.1%	(rectal cancer = 41.8%)
Crude	42.4%		Corrected	48.7%	
	51.4%			60.8%	

prognosis in anal canal and anal margin disease taken together is slightly better than rectal cancer. Unfortunately I cannot find any figures in the literature on the prognosis of the two sites taken separately.

If the five-year survival rate is broken down for site, that is into anal canal and anal margin tumours, the figures show that the prognosis of anal margin disease is more favourable than in anal canal cancer, the crude five-year survival rate for anal margin cancer being 51.4% and for anal canal cancer 42.4%. Moreover, this better five-year survival occurs despite the fact that most anal margin tumours were treated by local excision whereas the majority of anal canal cancers had a radical operation, with complete removal of the hæmorrhoidal lymphatic glands. In at least 75% of our cases of anal margin and anal canal cancer there was no treatment directed towards the inguinal gland method of spread either by surgery or radiotherapy. It is probable that the prognosis of anal cancer could be improved if a more radical approach to the inguinal gland spread could be devised.

Acknowledgments.—I would like to pay a tribute to the past and present surgeons of St. Mark's Hospital and in particular to Mr. W. B. Gabriel; to the Records Officer and follow-up organization; and to Dr. Cuthbert Dukes and Mr. H. J. R. Bussey for the painstaking work over the past thirty years which has made it possible to analyse such a relatively large number of cases of what is, after all, an uncommon disease.

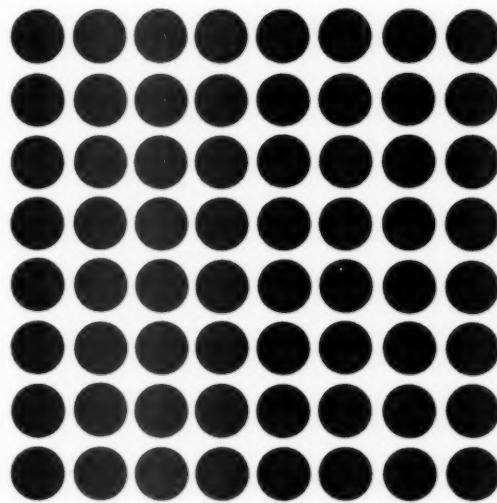
The expenses of this research were obtained from a block grant to the Research Department of St. Mark's Hospital by the British Empire Cancer Campaign.

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Meeting
February 3, 1960

The History of Sleeping Sickness in the Sudan

By J. F. E. BLOSS, D.P.H., D.T.M.&H.¹

THE epidemic of *Trypanosoma gambiense* sleeping sickness which broke out in central Africa at the end of the nineteenth century occurred in the early stages of European occupation of the continent. International boundaries were largely indefinite, and the Belgian occupation of an area along the Nile north of the Great Lakes complicated the occupation of the Sudan by Great Britain and Egypt in 1898. This area, known as the Lado Enclave (see Fig. 1), by treaty remained under Belgian authority for the lifetime of King Leopold I, who died in 1910.

Sleeping sickness had been recognized on the West Coast for over a hundred years, but it was unknown in central Africa until the late nineteenth century when, between 1896 and 1906, over half a million people were said to have died from the disease in the Congo, and in Uganda between 1898 and 1908 two-thirds of the population along the north west shores of Lake Victoria died.

The Sleeping Sickness Commission of the Royal Society arrived in Uganda in 1902 and were joined a year later by Colonel David Bruce. Castellani had by then identified a trypanosome from the cerebrospinal fluid of one of the patients, and this finding, with Bruce's experience of trypanosomiasis in animals led to the completion of the life history of the parasite and the finding of the vector, *Glossina palpalis*.

This knowledge enabled the Commission to establish the main principles for the control of the disease. These were, firstly, the need to break the man-fly contact either by mass movement of the people or by clearing vegetation so that the natural habitat of the fly was destroyed. Secondly, the extensive clinical research of the Commission proved the value of gland puncture for early diagnosis of the disease, and the need for mass examination of the population so that early cases could be detected.

Trypanosomes were first found in animals in the Sudan in 1904, and in 1905 the Sudan Government appointed its own Sleeping Sickness Commission to examine and report on the situation along the southern borders. Lieut.-Colonel D. Hunter, D.S.O., P.M.O. of the Sudan, was the first president, and Dr. Andrew Balfour, Director of the Wellcome Tropical Research Laboratories, the first member. The others, appointed later, were all members of the R.A.M.C. who were serving with the Egyptian Army in the Sudan. Their parish was the Bahr el Ghazal province extending from Raga in the west, to Shambe on the Nile, and southwards to the Nile Congo divide, an area of over 100,000 square miles, without roads and but sparsely administered. With so many recent changes of government, co-operation from the inhabitants could hardly be expected. To reach the province took up to six weeks from Khartoum and during the first



FIG 1.—Sketch map of the Southern Sudan and adjoining territories.

¹Deputy Director, Ministry of Health, Sudan Government, 1953-54.

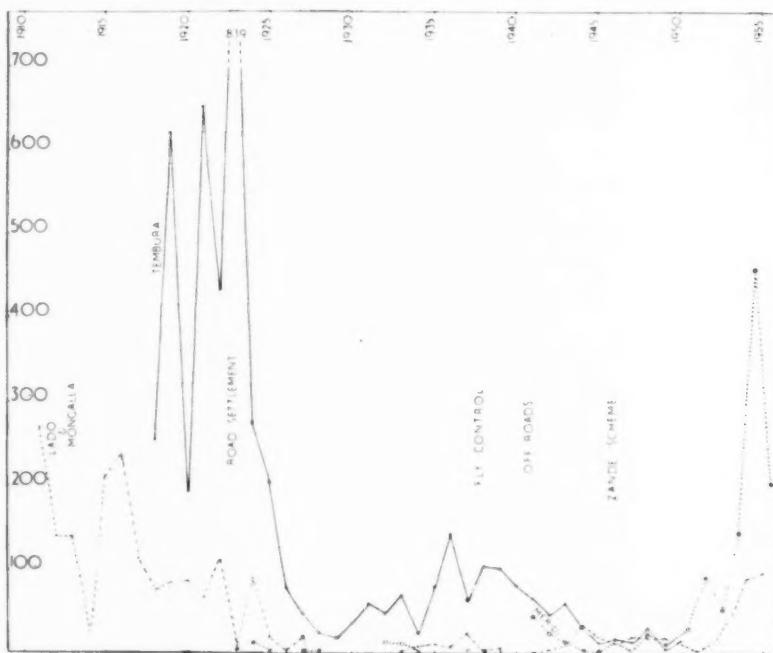


FIG. 2.—Annual number new cases sleeping sickness, 1910-1956, in affected areas of the Sudan.

five years there were but rarely more than two or three members of the commission in the area at any one time.

Between 1906 and 1909 several thousand people were examined but no cases found. The distribution of the two species of fly, *G. palpalis* and *G. morsitans*, was mapped out, and the seasonal variations and possible food sources of the fly were studied. This work was published in remarkable detail in the *Journal of the Royal Army Medical Corps*, the *Bulletin of the Sleeping Sickness Bureau* and the 2nd, 3rd and 4th Reports of the Wellcome Tropical Research Laboratories.

The Sudan Commission established that the disease could occur along the southern border of the Bahr el Ghazal province, and that the northern limit of *G. palpalis* did not extend far north of the border. Although no cases were found in the Sudan, they were recorded in the Belgian forts close to the border, to which, as medical men, they had access for the treatment of the Belgian officers and troops. In his report on the work of the Sudan Sleeping Sickness Commission for 1907-8 Ensor states "we may be, and probably shall be, unable to prevent sleeping sickness from crossing the frontier into the

Sudan, but with care we ought to be able to limit its spread". The general precautions he advised were the clearing of watering places and road river crossings, the strict control of porters and carriers, the segregation of cases if, and when, found, and the setting up of examination and inspection posts at strategic places.

The first human cases in the Sudan were found at the examination post of Raga on the French-Sudan frontier in immigrants and traders' carriers. Between 1909 and 1927, 73 cases, all infected outside the Sudan, were detected at Raga, but the comparative absence of *G. palpalis* in this area prevented the disease becoming established.

In 1908 it was known that cases were occurring inside the Lado Enclave. On June 16, 1910, this territory was taken over by the Sudan and the disease was soon diagnosed in and around Yei. In the first year Major C. Mackenzie, Colonel R. J. C. Thompson, and Yuzbashi Yusef eff Darwish (one of the most able of the Syrian doctors who did so much for the Sudan in its early days) mapped out the fly distribution, examined over 14,000 people in and around Yei, and found 218 cases of which 191 were in the

first stage of the disease, 19 in the second and 8 in the third.

Within a year an area of 120,000 square yards had been cleared near Yei as a segregation camp for cases: a census of the people had been started, and porters from the Congo or Uganda were banned. The traders' route from Rejaf on the Nile, through Loka and Yei, to the Congo was closed, and watering places and road river crossings cleared. In the first three years 547 cases were found, all within a 35-mile radius of Yei; thereafter the number of cases never rose above 32 per year.

In 1914 a further outbreak was discovered at Kajo Kaji close to the Nile, and extending to the east bank of the Nile at Opari. While the Yei outbreak was undoubtedly due to infection from the Congo, the Kajo Kaji and Opari outbreaks were due to infection from Uganda. These latter outbreaks were controlled by the usual precautions of clearing, making a census of the people, routine inspections, and restriction of traffic through the area. The wider area of spread of the disease and the difficulty of controlling traffic along the river made control of the Kajo Kaji outbreak more difficult, but by 1929 the old Lado Enclave and Mongalla Province were free of cases (Fig. 2).

In the south-west corner of the Sudan a far more serious outbreak occurred in 1918. From Tembura to Meridi the people are the Azande, one of the largest tribes in Central Africa. Evans Pritchard has estimated their numbers to exceed over two million, of whom 200,000 are in the Sudan, the remainder being in the Congo and French Equatoria. They are a purely agricultural people growing a large variety of crops, and with a great knowledge of the natural food sources of the forests in which they live. Their agriculture is primitive in that it is "shifting," but they normally produce enough for their needs. Witchcraft and magic dominate almost all the major and minor crises of their lives. Partly because of their agricultural needs in the way of land, and partly because of superstition, they live in homesteads usually some distance from each other and they were, therefore, difficult to contact and far from co-operative.

In 1916 the authorities in French Equatoria sought the aid of troops from the Sudan to quell a rising in their area. Some 800 levies from Tembura, accompanied by a R.A.M.C. officer, went to the aid of the French, and on their return there were undoubtedly cases of sleeping sickness among them. In 1917 thousands of French Azande crossed the frontier to take up residence in the Sudan. One party reached Raga where 31 cases of the disease were discovered and another 8 were diagnosed in a party

which reached Wau, but the majority settled just over the border around the Government post at Tembura. No cases were found in Tembura in 1917, but when Yuzbashi Nesib eff Baz, another Syrian medical officer, arrived at Tembura in March 1918, he found 60 cases within the first week, and 255 in his first six months without ever leaving his station. All but 12 were recent immigrants from French territory. In August 1918 he was joined by Captain B. H. B. Spence of the R.A.M.C. In the station at this time were these two medical officers, a District Commissioner who supervised both Tembura and Yambio, and a military officer. There were two main roads from Tembura, one to Wau, 200 miles north, and the other to Yambio, 150 miles to the east, both of which were overgrown for most of the year.

In 1919 these two doctors toured the district and found the epidemic was limited to the Tembura area along 50 miles of the border and 621 cases were found. They made a census of the people, cut new roads, built bridges, and with wheel and compass compiled maps of some 5,000 square miles of the country. They built a segregation camp at Tembura for the patients, housed and fed them, and cleared watering places and road river crossings.

At the end of 1919 Spence went on leave and Baz was left alone. In January 1920, Captain Watson, D.S.O., M.C., arrived, but within three days died as a result of an injury sustained on the journey. Spence and Baz had conceived the idea of a self-supporting settlement for the cases away from the administrative centre and close to the French border. Approval was obtained and on February 20, 1920, Baz with his staff and 669 patients set off on the 23 miles trek to the Sources Yubu Settlement. When they arrived they found the initial working party had prepared a site on the wrong side of the frontier.

Therefore grass had to be cut, roads made, huts built, watering places and streams had to be cleared and 150,000 lb of grain was brought by carriers from Yambio, 150 miles to the east. Baz's achievement can be measured by the fact that as long as there was food no cases deserted. In October inspections were started again. In many areas bicycles could now be used so that the task of inspections was eased, but the increased work meant that one medical officer had always to be in the settlement. By the end of September 1921, 1,517 cases had been admitted.

The success of the settlement led the authorities to hope that the organization of the people into villages would not only be possible but would facilitate sleeping sickness control. The Zande chiefs met this proposal with passive resistance and the simple cunning of never under-

standing precisely what was wanted, or where, or when. The scheme therefore had to be abandoned and inspections in 1922 showed a further spread of the disease to the north and east.

By February 1923, when Spence returned, the administrative staff had been increased with a second District Commissioner and it was decided to collect the people, not in villages, but on roads sited as far as possible along the water-sheds. Each subchief was to bring his own people to the road, to make and maintain their own length of the road with the clearing of river crossings and other watering places. A census roll was made and each adult tax-payer was issued with a numbered disc. All sleeping sickness regulations were, as far as possible, to be carried out through the authority of the chiefs. The ruling chiefs of the Zande belong to a special clan, almost a royal lineage, respected, feared and obeyed by the common rank and file. It was their support, as much as the full co-operation between the doctors and District Commissioners, that made the scheme the success it was. To permit settlement on the roads more roads had to be made. Inspections were the easier, more people were seen, and the census of the population increased by 15,000. It is therefore not surprising that, in 1923, 839 new cases were detected, the highest ever in the Sudan. The move to the roads proved popular for it opened up the district, eased administration, and regular three-monthly inspections of the people enabled cases to be detected early. By 1929 the annual number of new cases had dropped to 18.

The largest number under treatment in the settlement at any one time was 1,837 (in 1925). Between 1920 and 1929, 3,630 cases had been admitted, of whom 1,661 died (45.6%). Maurice (1930) points out that the multitude and variety of other tasks prevented clinical research. His closing words were true, but optimistic . . . "In the course of the campaign against sleeping sickness the habits of the natives were transformed. . . . The task of extirpating a disease had profoundly affected the life of a people."

The success of bringing the people to the roads led to similar administrative action in the adjoining Yambio district, and westwards as far as Meridi. By 1930 it must have appeared that the disease had been conquered for the only new cases were the few from the Tembura area. In the following years the incidence in the Tembura area started to increase, a few sporadic cases were found in Yambio and the Mongalla areas again showed one or two cases a year, but there was no great epidemic. The next stage, therefore, appeared to be an attempt to eradicate the infection.

Up to this time, control of the disease had

depended on removing man from the fly. It had succeeded in controlling epidemic conditions but it was no more than a retreat from an insect. Mr. C. B. Symes visited the sleeping sickness areas in 1937 and discussed the practicability of his "Block" method of *G. palpalis* control. Unlike *G. morsitans*, *G. palpalis* always stays very close to water and will not travel far from shade. The adult fly lives for six to nine months, and the female is larviparous, laying six to nine larvae during that time. It is one of the wonders of the insect world that the species has survived. Apart from the havoc of human disease and death that the tsetse has brought, it has been, and still is, a dominating influence on the habits and customs of the people over one-third of the African Continent.

The principle of the "Block" method of control is simple. The river is divided into sections, or Blocks, between each of which is a large clearing 800 yards long, and 200 yards wide on each side of the river. All trees and vegetation are cleared from this area, which then acts as a barrier so that fly from one section of the river will not move out of that section. Paths are cut along each side of the main river and of all the tributaries in that section and the hand catching of flies is started. When the density of fly in the first section is low a maintenance squad of fly catchers is left in that section and a mass fly-catching assault is made on the next section. By this means the fly population along the river is reduced, in stages, to a negligible level. In the Sudan we found that it was impossible to eradicate fly altogether, but with maintenance fly catchers it was possible to keep the fly incidence at an extremely low level. Provided control over the number of cases was also maintained, the area was then virtually safe.

Fly control schemes, based on this method of control, were started in the Yei and Tembura areas. For some time it had been noted that two-thirds of the cases in the Tembura District came from the Yubu river and the immediate vicinity of Tembura. This area was reasonably compact, and the river itself was considered ideal for an experiment in fly control.

There is inevitably a lag period before any results are seen in this type of control. The delaying factors are, first, the time needed to make the clearings and the fly-catching paths; secondly, the time taken to reduce fly numbers; and thirdly, the long incubation period of the disease, for cases are not easily detected much under a year after infection.

The "Block" scheme started along the Yubu river in 1938, and was completed by the beginning of 1941. By 1943 the fly catches were so

low that the barrier clearing of Block IV, beyond which there was no fly catching, was the only one we felt it was necessary to maintain thoroughly cleared. At the height of the scheme 220 fly boys were employed with three Sudanese public health officers in charge of the groups into which the boys were divided. They lived in special camps built in the sections and each month they came into the Yubu settlement for their pay, food, and the prizes awarded to those who caught the most flies. The proportion of cases in the Tembura district, attributed to the River Yubu, decreased to under 50 per cent in 1940, and by 1942 there were only 3 cases from the fly control area out of a total of 44 in the whole of the Tembura district.

Because of the war it had become increasingly important to remove any unnecessary restrictions and, if possible, to permit the people to cultivate as and where they wished. In 1940 all restrictions were removed and the chiefs agreed to undertake the necessary maintenance work in the fly control area. The Azande had gained their freedom of residence and we felt that we had evolved a method of control of the disease.

In 1943 Dr. J. D. Tothill, Director of Agriculture, visited Zande District and put forward a scheme for the development of the area. This was based on the growing of an economic crop (cotton), and the resettlement of the people in permanent family and group farms, so that not only an economic crop, but increased crops of other foods could be grown. A ginning, spinning and weaving factory was built, and a trading board under government sponsorship was established to provide cheap but attractive goods of all kinds. With the scheme went new schools, and an agricultural training college with facilities for research. Before it was completed the whole scheme cost over a million pounds. The task of moving the people began in 1946. Each family was given a plot of 30 acres, spaced along lines supervised by their headman. By 1951, 48,000 families had been resettled, new homes built, crops sown, and in some cases two or three rich harvests reaped, all of which was accomplished in an area of some 25,000 square miles by gentle persuasion and, what is more important, quickly, cheerfully and freely by the Zande themselves. A new town, Nzara, with the factory, had also been built close to Yambio.

Wartime restrictions had reduced the number of doctors in the area, and the work of the development plan gave all medical staff increased commitments. Sleeping sickness was fortunately at a very low level, but inspections continued to be carried out annually. The resettlement of the people in many ways helped administration and

medical work and the fact that the new farms crossed or bordered on many fly-infested streams was realized to be a possible risk. The success of the scheme, and the variety and worth of goods on sale in the shops, encouraged Zande friends and relatives from the Belgian side to cross the frontier and change their allegiance.

Abbott (1952) has pointed out that the incidence of sleeping sickness in the adjoining district of the Belgian Congo was higher than in the Sudan, and it is reasonable to suppose that among those who crossed the frontier were some incipient cases of sleeping sickness. The industrial, educational and administrative area around Yambio, Nzara the new town, and Li Rangu, the hospital and medical centre, became far more thickly populated than ever before. Between 1946 and 1950 there were 60 cases of sleeping sickness: in 1951, 98 new cases were found but numbers fell to 53 in 1952. In the year 1953-54 the new cases exceeded a hundred.

This new epidemic involved several rivers within a twenty-five miles radius of Yambio, all known to harbour fly. Even if staff had been available comprehensive fly control throughout the area would have been impracticable. Because of the development scheme mass movement of the people was impossible, and trade and traffic through the area could never be effectively controlled. Mass chemoprophylaxis with pentamidine had been of proved value in the Congo and elsewhere and this it was proposed should be the main line of attack in these conditions. Restricted fly control schemes in selected areas, and a fly survey to determine density along the rivers from which cases had been found were subsidiary measures designed to prevent further spread of the epidemic.

The value of pentamidine prophylaxis is three-fold. Firstly it sterilized the blood stream of trypanosomes, secondly, it therefore reduces the hazard of flies becoming infected, and thirdly, if man is attacked by an infected fly the trypanosomes inoculated have less chance of survival. The principle of the campaign was not eradication of the disease with restrictive measures, but control of the epidemic and the reduction of its incidence to negligible proportions.

The political scene in the Sudan was changing rapidly and eventually this scheme was implemented with the assistance from the World Health Organization, the first occasion on which that body had assisted in sleeping sickness work. They had hardly commenced when, in June 1955, administrative troubles disrupted government in the southern areas. The delay in starting caused a further increase in cases, and when the work finally began the incidence almost rivalled the worst periods of the Tembura outbreak.

Conclusions

By 1910 the central African epidemic of sleeping sickness had invaded the Sudan through the Lado Enclave, but as this epidemic spread north its rate of spread and its severity waned. The Sudan Sleeping Sickness Commission was able to assess probable areas of spread inside the Sudan as a result of fly surveys they carried out. Such surveys have been continued and Lewis (1951) published a map of the distribution in the Sudan of all known species of *Glossina*.

The Tembura outbreak, 1918-1940 was the largest in the Sudan and the most difficult to control. The initial measures were necessarily restrictive on the life of the people, and it was not until fly control schemes were introduced that it was possible to remove these restrictions.

T. gambiense sleeping sickness is essentially a disease of a particular environment, the environment of *G. palpalis*. Abbott has pointed out that the limits of the fly are not coterminous with those of the human disease. Climatic, vegetative, and seasonal differences cause variations in the fly density and in the conditions under which the man-fly contact can occur. The Sudan border is close to the northern limits of *G. palpalis* and these factors account for the variations in the epidemiology in the Sudan and elsewhere.

Human sleeping sickness has been one of the major tropical epidemics and like the major epidemics of temperate climates it is important to realize that its control has depended, and still depends, on public health—environmental medicine—rather than on clinical medicine. There can be few diseases where it is necessary to have such a versatile and all-round knowledge of the vector, the people, their language and customs, the fauna, the flora, and the geography of the area.

We must not forget that the early workers tackled a killing epidemic of unknown aetiology in unknown territory. As the cause and vector were known so the need for a full knowledge of the environment became appreciated. The principles of control they established then apply equally to-day, though we may apply them with different techniques. The breaking of the man-fly contact and the search for early cases by mass examinations of the whole population are still of prime importance. The frequency of mass examination and the methods of fly control may have changed, and the advent of chemoprophylaxis has made control possible without the need for drastic restrictions on the life of the population. Indeed modern methods of control make social and economic progress possible.

In the Sudan no praise can over-estimate the

work of the British and Syrian military medical officers of the Sudan Sleeping Sickness Commission. They were the pioneers of medicine in the southern Sudan and, overcoming the natural reserve and lack of co-operation from the inhabitants, laid the foundation of future success. The British and northern Sudanese doctors who followed were able to work among a population that by comparison was fully co-operative. Eventually sleeping sickness was brought under control and the economic and the post-war development scheme of the infected areas was made a practical possibility.

The story of sleeping sickness in the Sudan is but a small part of the history of the disease in Africa, but notwithstanding its special conditions a study of that history emphasizes the great achievement of the early workers and—lest we forget—the seriousness of the infection. As long as cases exist so the danger of an epidemic exists.

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Meeting
January 27, 1960

Studies with 19-Norethisterone *Œ*nanthate in Mammary Carcinoma

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VARIOUS investigators including Epstein *et al.* (1958) and McGinty and Djerassi (1958) have reported that 19-norethisterone is capable of inhibiting gonadotrophin production in experimental animals. Estrogenic effects have also been noted after administration of the compound, and it has been suggested (McGinty and Djerassi, 1958) that estrogen production in the body may be responsible for the inhibition of pituitary gonadotrophin secretion. If these claims are correct, and if norethisterone is indeed capable of inhibiting pituitary function, it is possible that the drug might have some place in the palliative treatment of mammary cancer in humans.

This report concerns the value of 19-norethisterone *Œ*nanthate (19NEO) in the management of recurrent and metastatic mammary carcinoma. Studies made on the pharmacological effects of the drug in the same group of patients are also described. A purely clinical study was carried out on a further group of patients in the Radiotherapy Department in Edinburgh, but no further reference will be made to this second group other than to state that the clinical findings confirmed those now reported.

Materials and Methods

The present series of patients consisted of 12 women with recurrent or metastatic mammary carcinoma. In addition to clinical and radiological examination the following investigations were also undertaken.

(1) *Pituitary gonadotrophin excretion* before and during treatment with 19NEO. The assay method used was that of Loraine and Brown (1959).

(2) Limited studies on *œ*strogen excretion (Brown *et al.*, 1957), total 17-oxosteroid excretion (Vestergaard, 1951) and total 17-hydroxycorticosteroid (17OHCS) excretion (Appleby *et al.*, 1955).

(3) *Vaginal smears*, taken before and after treatment.

(4) *Thyroid function*, as assessed by estimations of serum protein-bound iodine (PBI) (Zak *et al.*, 1952) before and after treatment, as well as by studies with ^{131}I (Fraser *et al.*, 1953).

(5) *Serum calcium and alkaline phosphatase* estimations, and *urinary calcium estimations* were also made when there were grounds for suspecting that active bone disease existed.

(6) In two patients full metabolic balance studies were carried out in order to determine whether the drug had any anabolic or other metabolic properties.

The clinical findings in the group of 12 patients in whom these studies were performed are summarized in Table I. The distribution of recognizable tumour tissue was widespread in most of the patients at the time of study, and provided adequate evidence for assessing the effect of the drug on the disease.

Most of the investigations described were carried out during an initial period of observation in hospital. Treatment then commenced with weekly injections of 19NEO, each of 200 mg, except in one patient (Case 12) in whom the dose was approximately 560 mg weekly. Patients were then discharged from hospital if they were sufficiently well provided for at home, and they attended each week for further injections. In most cases, urine collections continued at weekly intervals at home, so that serial observations could be made on hormone excretion during the course of treatment.

Results

The effect of weekly injections of 200 mg 19NEO on the excretion of gonadotrophins is shown in Table II, and typical examples are illustrated in Figs. 1 and 2. Gonadotrophin excretion before treatment varied in different patients between 128 and 4 HMG units per twenty-four hours, but during and after treatment this was reduced in most cases to less than 10 units per twenty-four hours.

It should be pointed out that in one only of the patients described (Case 10) was there evidence of remission of disease, and the effect of treatment on the excretion of gonadotrophins in this patient was similar to that in the other patients in the series.

In the 2 patients studied, the excretion of 17-

TABLE I.—DISTRIBUTION OF DISEASE IN 12 PATIENTS STUDIED.
The only patient to show a favourable response to treatment was Case 10.

No.	Initials	Age	Years past menopause	Interval between operation and observations (months)	Primary tumour present	Skin		Glands		Lungs	Pleura	Skull	Ribs	Pelvis	Spine	Liver
						Local	Metastatic	Local	Metastatic							
1	J. B.	49	9	13	+	+	+	+	+	+	+	+	+	+	+	+
2	E. McK.	65	18	16	+	+	+	+	+	+	+	+	+	+	+	+
3	A. H.	58	5	16	+	+	+	+	+	+	+	+	+	+	+	+
4	H. W.	50	7	84	+	+	+	+	+	+	+	+	+	+	+	+
5	H. S.	85	38	+	+	+	+	+	+	+	+	+	+	+	+	+
6	J. B.	70	≥ 20	23	+	+	+	+	+	+	+	+	+	+	+	+
7	M. T.	76	31	27	+	+	+	+	+	+	+	+	+	+	+	+
8	G. W.	74	24	+	+	+	+	+	+	+	+	+	+	+	+	+
9	C. K.	58	18	114	+	+	+	+	+	+	+	+	+	+	+	+
10	C. M.	54	7	57	+	+	+	+	+	+	+	+	+	+	+	+
11	C. W.	66	16	102	+	+	+	+	+	+	+	+	+	+	+	+
12	E. D.	74	22	37	+	+	+	+	+	+	+	+	+	+	+	+

oxosteroids and 17-hydroxycorticosteroids did not alter during treatment with 19NEO.

Vaginal smears were taken before treatment and at the end of treatment in each of the patients studied. With one exception, the smears before treatment showed the typical postmenopausal appearance, but the changes found after treatment were very variable. In some, almost complete "oestrogenization" of the smear apparently occurred, whereas in others there was little change. The behaviour of the smear in one patient who improved during the trial was in the intermediate range of responses seen, and showed

slight evidence of an oestrogenic response after almost six months' treatment.

Thyroid function was reviewed before treatment started, and again at the end of treatment, or at least six weeks after the initiation of treatment. The serum concentrations of protein bound iodine (PBI) before and after treatment in the 5 patients for whom paired observations are available are shown in Fig. 3. It is noteworthy that one patient fell within the hyperthyroid range. She had a large goitre of long standing, and on clinical grounds was definitely thyrotoxic. A second patient was equally clearly hypothyroid,

TABLE II.—GONADOTROPHIN EXCRETION (HMG UNITS/24 h) BY PATIENTS TREATED WITH 19NEO

CASE NO.	GONADOTROPHIN EXCRETION BEFORE TREATMENT	WEEKS OF TREATMENT									1 yr.
		1	2	3	4	5	6	7	8	9	
1	78, 78, 80	65, 60	21	< 10	9	→					
2	4, 8, 19	< 16	< 17	< 10	33	→					
3	65, 83, 70, 73	32	< 8		< 10	8	< 10 _b	7	6		
4	43	20, < 15	< 5	< 8	5	→					
5	77, 126, 75	54, 24	20	5	6	5	10				
6	84, 84, 24	34	26	24	32	21	→				
7	34, 26, 60, 34	31	20, 13	13	14	10	8, 10	10	10		
8	38, 32, 26, 28	52	8	18	8, 8	9, 5	5, 5	10, 7	6, 5		
9	122, 144										
10	42, 40, 32		7								→ 1 yr.
11	39, 47, 40, 49			14	6	10, 8					
12	73, 128	48, 52	32, 12	20	11	5	5	8	10		
		1	2	3	4	5	6	7	8	9	

(Note 1. In Case 10, results after treatment for six months were consistently < 6 HMG units/24 h.

2. Case 12 received 560 mg 19NEO weekly.
3. → duration of treatment.)

but during the period covered by these observations neither received any treatment for the disorder of thyroid function. In each instance, the concentration of PBI fell during the period of treatment, and although there are only five pairs of observations, yet the difference between the means was found to be significant ($P < 0.05$).

The results of ^{131}I excretion tests showed no consistent change attributable to treatment.

In one patient only was there evidence that the progress of the disease might have been accelerated by the treatment, though these findings might conceivably have been coincidental. The results of serum and urine calcium studies in this patient are shown in Fig. 4. The serum calcium concentration was raised, and the excretion of calcium in the urine was increased after a brief period of treatment with 19NEO.

Metabolic balance studies were carried out in 2 patients. Throughout the period of study the patients were on a constant intake consisting basically of Complan, and in the first patient (Fig. 5) it is evident that administration of 19NEO was not accompanied by any consistent change in nitrogen, calcium, sodium, potassium or chloride excretion in the urine. In the second patient (Fig. 6), who received 560 mg 19NEO weekly, there was evidence of slight retention of nitrogen but the changes were relatively trivial.

Discussion

Although one patient obtained a satisfactory remission of disease while being treated with 19NEO, the drug compares unfavourably with a number of others used in the management of advanced breast cancer, and it is unlikely there-

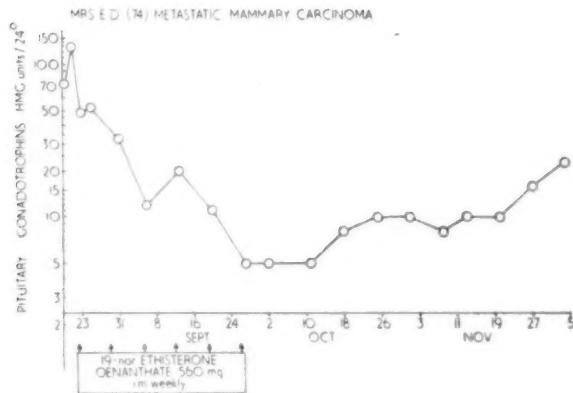


FIG. 1.

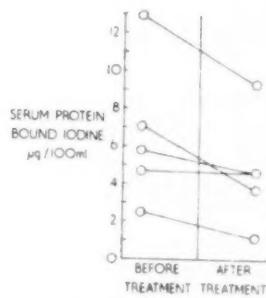


FIG. 3.—Changes in serum protein-bound iodine during treatment with 19NEO. Analysis of significance: $t = 2.87$ ($0.05 > P > 0.02$).

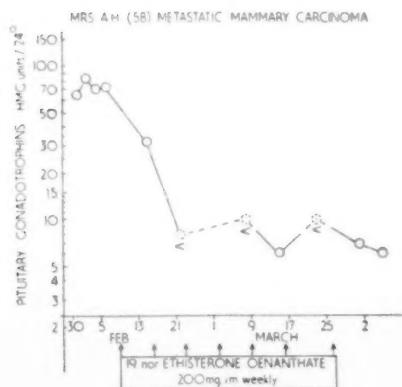


FIG. 2.

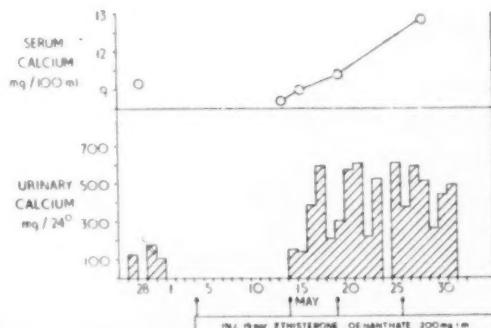


FIG. 4.—Changes in serum calcium concentration and in urinary calcium in Case 11 (Mrs. C. W., aged 66, metastatic mammary carcinoma) who deteriorated rapidly during treatment with 19NEO.

fore to find a place in the management of this disease in the postmenopausal patient.

Gonadotrophin excretion was consistently reduced by treatment with 19NEO. Before treatment the amount excreted daily by this group of patients was similar to that found in the majority of women in this age group. It may be noted, however, that in contrast to the findings during treatment with stilbestrol, gonadotrophin excretion after 19NEO was reduced only to premenopausal levels, rather than abolished completely, or reduced below the level which could be measured by the method in use. Even in Case 12, when the dose of 19NEO used was three times greater than in the other patients, the excretion of gonadotrophins was still not abolished.

In 3 of the patients described estimations of pituitary gonadotrophins in plasma were carried out before and after treatment with 19NEO. In each instance the assays showed a fall in plasma activity after treatment to levels below that at which activity could be detected (Apostolakis, 1959).

Estrogen excretion by patients treated with 19NEO increases very considerably (Brown and Blair, 1960). The changes in the appearance of the

vaginal smear in some of those patients would indicate that this oestrogen is biologically active, but the response was remarkably inconsistent, and in some patients was virtually absent. It is possible that the effect on the pituitary and the reduction in the excretion of gonadotrophins are due to the formation of oestrogenic metabolites from 19NEO, but if this is indeed the case, the changes in the vaginal smear might be expected to be as consistent as the reduction in gonadotrophin excretion. This consistency was not found.

In 2 patients studied the excretion of 17-oxosteroids and 17-hydroxycorticosteroids was not reduced during treatment with 19NEO. It seems unlikely therefore that the secretion of pituitary ACTH was depressed by this treatment.

The depression of serum protein-bound iodine concentration during treatment with 19NEO may have been due to several possible causes. It is unlikely that this effect resulted from suppression of the secretion of pituitary thyrotrophic hormone since, if this had been so, radioiodine metabolism would have been depressed in the same way as the serum PBI was reduced.

Limited metabolic balance studies in 2 patients

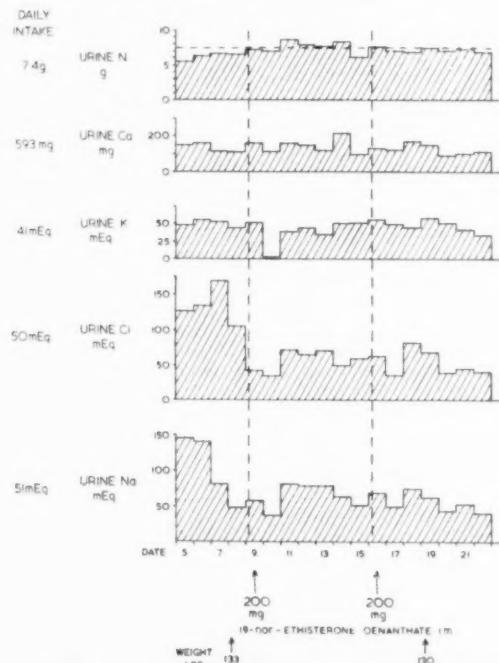


FIG. 5.—Metabolic balance study in Case 5 (Mrs. H. S., aged 85, mammary carcinoma) given two injections each of 200 mg of 19NEO at an interval of one week.

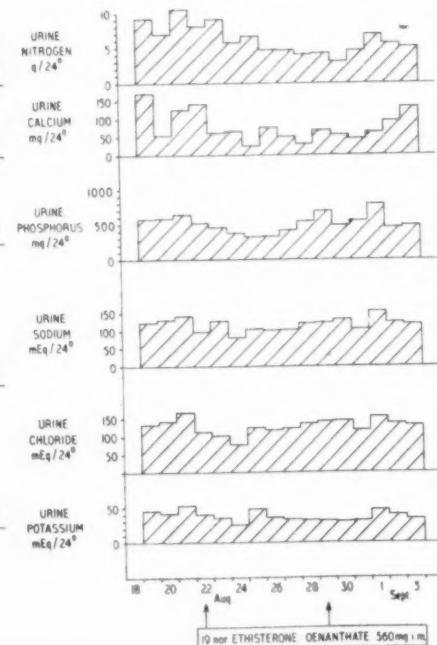


FIG. 6.—Metabolic balance study in Case 12 (Mrs. E. D., aged 74, mammary carcinoma) given two single injections each of 560 mg of 19NEO.

suggested that 19NEO was devoid of any marked action on nitrogen, phosphorus, calcium, sodium, potassium or chloride metabolism.

Summary

12 patients with advanced breast cancer were treated with weekly injections of 200-600 mg of 19-norethisterone α -enanthate; of these, one patient only showed a favourable response, and remains under treatment. Gonadotrophin excretion was reduced during this treatment in all patients studied. Observations are reported on the effect of 19NEO on the excretion of oestrogens, 17-oxosteroids and 17-hydroxycorticosteroids, on the vaginal smear, on thyroid function and on metabolic balances.

Acknowledgments.—Our thanks are due to numerous colleagues who helped in many ways with this study, especially Professor Robert McWhirter. Messrs. A. G. Schering, Berlin, provided the steroid used.

The Effect of 17 α -Ethinyl-19-Nortestosterone (Norethisterone) on the Urinary Excretion of Oestrogens, Pregnanediol and Gonadotrophins during the Menstrual Cycle [Abridged]

By J. B. BROWN, M.Sc., Ph.D., K. FOTHERBY, B.Sc., Ph.D., A.R.I.C., and J. A. LORAIN, D.Sc., Ph.D., M.R.C.P.Ed.

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THE pattern of the urinary excretion of oestrogens, pregnanediol and gonadotrophins throughout nine ovulatory menstrual cycles has been described previously (Brown *et al.*, 1958). The present communication describes the excretion of these substances by two subjects with dysmenorrhoea and one subject with premenstrual tension, before, during and after treatment with norethisterone or its acetate.

The subjects were healthy and were normally active during the periods of investigation. Rectal temperatures were recorded each morning on awakening. Urinary pregnanediol was estimated by the method of Klopper *et al.* (1955) and urinary gonadotrophins by the method of Lorraine and Brown (1959). Urinary oestrone, oestradiol and oestriol were measured by the methods of Brown (1955) and Brown *et al.* (1957). Urinary metabolites of norethisterone and its esters interfere in these methods causing the oestradiol values by both methods and the oestrone values by the latter method to be high; they do not, however, interfere with the determination of oestriol (Brown and Blair, 1960).

The first subject, who had regular menstrual cycles with severe menstrual and premenstrual dysmenorrhoea, was studied throughout four menstrual cycles. The results are shown in Fig. 1. During the first cycle in which she did not

We are greatly indebted to the Melville Trust for generous financial support for part of this research programme.

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receive any treatment the levels of oestrogen, pregnanediol and gonadotrophin excretion were within the normal range but there was no rise in gonadotrophin excretion at mid-cycle. The temperature chart was biphasic and there was a gain in weight premenstrually. There was severe dysmenorrhoea for three days premenstrually and menstruation lasted five days.

During the second cycle norethisterone acetate (6 mg per day) was administered orally from the fifth to the twenty-fifth day. The gonadotrophin excretion was similar to that during the first cycle. There was no rise in pregnanediol or oestrogen excretion during the second half of the cycle, although a peak of oestrogen excretion occurred at approximately mid-cycle. The temperature chart remained biphasic and there was a gain in weight premenstrually. There was severe dysmenorrhoea for three days before menstruation and the latter lasted four days. The findings in this cycle are compatible with the view that luteal function but not follicular function was depressed by the administration of norethisterone acetate.

During the third cycle norethisterone acetate (12 mg per day) was administered orally from the fifth to the twenty-fifth day. Oestrogen and pregnanediol excretion remained fairly constant throughout the cycle. Gonadotrophins were excreted throughout the cycle with possibly a

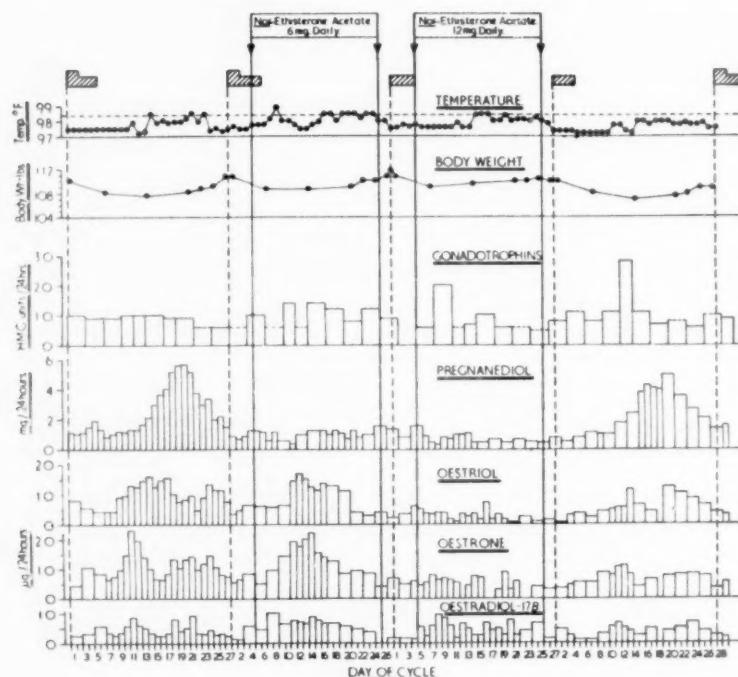


FIG. 1.—Miss D. M., aged 27, para-0, dysmenorrhoea. The excretion of oestradiol-17 β , oestrone, oestriol, pregnanediol and gonadotrophins and the variations in basal temperature and body weight. Gonadotrophin assays: A broken line indicates a result in which the reading is actually less than the figure shown. Hatched areas indicate menstrual periods.

peak of excretion about the eighth day. The temperature chart was still biphasic but there was neither dysmenorrhoea nor a premenstrual weight gain. The duration of menstrual bleeding was reduced and lasted only three and a half days. The findings in this cycle suggest that both follicular and luteal functions were depressed. It was surprising that the temperature chart in both this and the previous cycle remained biphasic since the administration of norethisterone usually has a hyperthermic effect (Pots, 1957).

The findings during the fourth cycle where no norethisterone was administered were similar to those in Cycle 1 except for the presence of a peak in gonadotrophin excretion at approximately mid-cycle.

In the other two subjects studied the administration of norethisterone (10 mg per day) or of its acetate (12 mg per day) from the fifth to the twenty-fifth day of the menstrual cycle prevented any rise in oestrogen and pregnanediol excretion. The excretion of gonadotrophins was not decreased during the period of treatment.

There seems to be no doubt from these results that norethisterone in a sufficiently large dose, administered from the fifth to the twenty-fifth day of the cycle, will prevent the rise in oestrogen and pregnanediol excretion which normally occurs during the luteal phase and the rise in oestrogen

excretion which normally occurs during the follicular phase. Smaller doses of norethisterone appear to inhibit the rise in the excretion of oestrogens and pregnanediol during the second half of the cycle without inhibiting the rise in oestrogen excretion during the follicular phase.

The excretion of gonadotrophins continued throughout each cycle and did not appear to be affected by the administration of norethisterone. It might be postulated therefore that norethisterone exerted its effect by a direct action on the ovary rather than through the pituitary. However, it has been shown that norethisterone decreases the gonadotrophin excretion of postmenopausal patients with mammary carcinoma (Douglas *et al.*, 1960) and inhibits the pituitary secretion of gonadotrophins in parabiotic rats (Epstein *et al.*, 1958).

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Urinary Oestrogen Metabolites of 19-Norethisterone and its Esters [Summary]

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INCREASES in urinary oestradiol values amounting to 10 µg/day, without corresponding increases in oestrone and oestriol, when measured by the method of Brown (1955), were observed in a subject given norethisterone acetate (12 mg/day orally). When a saponification step was incorporated in the method (Brown *et al.*, 1957), increases in both oestradiol and oestrone values of 8 and 13 µg/day respectively were observed without any change in the oestriol. Quantitatively similar results were obtained in all of 6 women given norethisterone or its acetate orally, or its oenanthate intramuscularly. Similar observations have been made by Parada *et al.* (1959) and by Breuer *et al.* (1960) who isolated and identified the oestrone following saponification. The failure of the oestriol to increase under these conditions shows that the increases in oestrone and oestradiol are due to an artifact derived from the norethisterone. Experiments showed that this was a metabolite of norethisterone and that it was not a ketone but was converted to oestrone on saponification. Engel *et al.* (1958) showed that 19-nortestosterone is converted *in vivo* to oestradiol and 0.03% of the dose is excreted in the urine as oestrone. The possibility was considered that norethisterone is similarly metabolized to ethynodiol. Ethynodiol gives one-tenth the intensity of colour given by oestradiol in the Kober reaction; when ethynodiol was added directly to urine and measured by the method of Brown, 50% was destroyed during acid hydrolysis and 30% was recovered in the oestradiol fraction without any appearing in the oestrone or oestriol fractions; when saponification was included, 22% was recovered in the oestradiol fraction and 8% was recovered as oestrone. These figures fit exactly those found following the administration of norethisterone and its esters. They also agree with those of Langecker (1959) who showed that ethynodiol, on boiling with alkali, is converted in 20% yield to oestrone with the liberation of acetylene. Therefore all the evidence indicates that ethynodiol is a metabolite of norethisterone. Further experiments showed that ethynodiol is not liberated by incubation with β -glucuronidase and phenolsulphatase (*Patella vulgata*) from the urine of individuals receiving norethisterone although it is liberated in increased yields (150% of acid hydrolysis) when ethynodiol itself is administered.

The amounts of ethynodiol excreted per day during the administration of ethynodiol and of norethisterone and its esters were calculated from the urinary oestradiol and oestrone values obtained following acid hydrolysis (Table I). The results indicated that a dose of 12–30 mg

TABLE I

Compound administered	Patient	Dose mg/day	Increase in urinary oestrone value µg/24 h (sap.- no sap.)	Calc. excretion of ethynodiol µg/24 h	Calc. dose of ethynodiol mg/day
Ethynodiol	A. B.	1	10	125	1
Norethisterone	P. B.	20	9	110	0.9
	M.	10	6	80	0.6
	M.	20	9	110	0.9
Norethisterone acetate	D. M.	12	7	90	0.7
	G. G.	12	13	160	1.3
Norethisterone oenanthate	E. D.	80	50	620	5.0
	C. M.	30	13	160	1.3

norethisterone is converted in the body to approximately 1 mg ethynodiol, 12.5% of which is recovered in the urine as ethynodiol. While norethisterone has oestrogenic properties, it does not appear to be as active in this respect as these doses of ethynodiol would indicate. Possible explanations for this might be that the conversion occurs in the liver and little of the ethynodiol reaches the general circulation before it is excreted; or the substance excreted in the urine is not ethynodiol but is converted to it during acid hydrolysis. However, the possibility that some of the biological properties of norethisterone and its esters, such as pituitary inhibition, might be due to conversion *in vivo* to relatively large amounts of a potent oestrogen should not be overlooked.

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Observations on the Clinical Uses of Some New Progestational Compounds [Abridged]

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In obstetrics and gynaecology the suggested indications for progesterone therapy include arrest of endometrial bleeding, conversion of the endometrium to a secretory phase in persistent proliferative states or in amenorrhoea, premenstrual tension, dysmenorrhoea, threatened or habitual abortion. To accomplish successful results in these conditions several possible modes of action can be postulated. The compound may act directly upon the endometrium affecting the bleeding mechanism or the cytological structure, and these two aspects are not interdependent because bleeding may be associated with any histological state of the endometrium whether normal or abnormal, whether proliferative or secretory. Secondly, there may be a direct action upon the pituitary with inhibition of gonadotrophic secretion. Thirdly, there may be a direct action upon the ovary, and lastly there may be more remote systemic actions affecting the symptoms of such conditions as premenstrual tension in which the underlying aetiological factors have not yet been determined.

There are two methods by which the value of progestational preparations can be assessed—by carefully controlled clinical trials, or by determining the rationale of therapy by scientific research or, more satisfactorily, by a combination of both.

The new progestational compounds can certainly arrest endometrial bleeding by inducing a "medical curettage", but this method seems to have no particular advantage over that in which oestrogens alone are used.

In amenorrhoea progestational compounds may produce secretory changes in an oestrogen-primed endometrium, but this response is not constant and is presumably dependent upon the dosage and the sensitivity of the target organ. However, there seems no advantage in establishing cyclical secretory changes in such cases without evidence that ovarian function is influenced to the extent of inducing a return to normal ovulatory cycles. The conversion of a proliferative to a secretory endometrium in cystic glandular hyperplasia is of limited and temporary value because there is no conclusive evidence that cyclical therapy with progestational agents will lead to ovulatory menstrual cycles.

It has been suggested that in infertility patients progestational compounds may be of value in correcting an inadequate luteal phase of the menstrual cycle. In my experience, evidence of deficient corpus luteum activity is found in 3%

of infertility patients, but only as an isolated occurrence. Repeated biopsy in subsequent cycles invariably shows a normal endometrium. Thus, in these cases, there is no real indication for such therapy and, as control is impossible, there can be no proof, not even by a successful pregnancy, that this treatment is of any value.

Being manifest largely by subjective phenomena, premenstrual tension is one of the most difficult conditions in which to assess results of therapy. If an altered oestrogen/progesterone ratio is an aetiological factor, there may well be a place for treatment by the progestational agents but it would be reasonable to suppose that added oestrogen or oestrogen conversion should vitiate results. Dysmenorrhoea is associated with the same difficulties as premenstrual tension in assessing the results of treatment. The totally unphysiological procedure of suppressing ovulation by these or other drugs is hardly a justifiable means of dealing with this or any other gynaecological condition.

It will be difficult to establish that these compounds play any part in preventing abortion. Animal experiments do not support this contention and masculinizing effects upon the female foetus suggest that more harm than good may sometimes result from their early and long-continued use.

The use of progestational compounds in clinical practice is confused and the preliminary results of research into their action have done nothing to clarify the position. These agents are having an effect upon the endometrium; they also suppress ovarian function if given during the menstrual cycle. What is not clear is their mode of action. Broadly speaking these compounds may be divided into two groups—those with, and those without, oestrogenic activity. To date, most research work has been concerned with the former group and it is impossible to assess to what extent their effect is due to the oestrogenic element, particularly in regard to pituitary suppression. Before recommending wide clinical use of these preparations their precise mode of action should be determined. In further research and clinical trials, unnecessary confusion which arises from using preparations known to have oestrogenic activity, either through added oestrogen or oestrogen conversion, should be avoided and, in the first instance, only compounds without an oestrogenic element but of proven progestational activity should be studied.

Meeting
February 24, 1960

COMBINED MEETING WITH THE SOCIETY FOR ENDOCRINOLOGY

Determination of the Relative Potency of Some Progestogens in the Human

By G. I. M. SWYER, D.M., LILLY SEBOK, M.B., and DOREEN FOURACRE BARNES, M.B.
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IN a survey of some of the problems involved in the clinical assessment of progestational agents (Swyer, 1960) it was suggested that since none of these agents possesses all the known properties of progesterone, and since the various properties are, in general, possessed in varying degrees, a number of different criteria should be employed for tests of comparative potency. The criteria considered were: (1) The production of subnuclear vacuolation in the endometrium following a five-day course of progestogen given to oestrogen-primed women with secondary amenorrhoea or amenorrhoea following castration. (2) The production of a mid- or late secretory endometrium in similar women following a ten-day course of progestogen, in both (1) and (2) two previous similar courses of oestrogen and progestogen having been given to sensitize the endometrium. (3) Withdrawal bleeding following a five-day course of progestogen in women with secondary amenorrhoea. (4) Postponement of menstruation in normal women given a twenty-day course of progestogen from the twentieth day of the cycle. (5) Depression of the karyopyknotic index in the vaginal smear. (6) Inhibition of the oestrogen-induced changes (including fern crystallization) in the cervical mucus of the patients mentioned in (1). (7) Inhibition of ovulation, which, it was suggested, might be determined by the ability of a course of progestogen given from the fifth to the twenty-fifth day of the cycle to produce a painless period in women complaining of "essential" dysmenorrhoea.

As a result of experience in trying to apply these criteria to tests of relative potency of progestogens in the human, it has become clear that there are formidable practical difficulties in the way of carrying out trials which would provide statistically reliable data. The most promising test is that involving postponement of menstruation (4, above), although the results obtained in this way do not necessarily agree with those obtained with tests (1) or (2). With these latter tests, however, statistical evaluation is not possible. This paper will consider our current data on postponement of menstruation, and will also refer to results obtained with withdrawal bleeding and to changes in the vaginal smear.

Postponement of menstruation.—Patients

attending the Fertility Clinic at University College Hospital and in whom no significant abnormalities had been detected on routine investigation were instructed to take the progestogen tablets orally from the twentieth day of the cycle for twenty days or until the period began, whichever was the sooner. If menstruation was postponed until after the completion of the twenty-day course, treatment was resumed on the twentieth day of the next cycle at half the previous dose; if it began before the completion of the twenty-day course, treatment in the following cycle was at double the previous dose. In this way, it was hoped to establish for each substance tested the dose which would be effective in 50% of patients and to provide the basis for probit analysis. The results to date encourage the belief that it will be possible to compare at least some progestogens by this means, and to establish potency ratios with fiducial limits of error. For this purpose, however, more rigidly-planned trials will be necessary and are at present in progress. For the moment, it can be said that a meaningful dose-

TABLE I.—POSTPONEMENT OF MENSTRUATION

Drug	Daily dose mg	No. of observations	% of positive responses	50% effective dose, mg
Norethisterone	20	11	100	4.25
	10	25	84	
	5	28	68	
	2.5	20	25	
Norethisterone acetate	2	3	0	10.25
	1.5	2	100	
	1.0	14	43	
	0.5	16	18.5	
	0.4	4	0	
Enavid	2	3	0	5
	1.0	6	83	
	0.5	13	46	
Dimethisterone	2.5	3	0	> 80
	80	3	0	
	40	8	0	
	30	2	0	
21-methyl norethisterone	20	5	0	10
	10	3	0	
	30	1	0	
21 MNE + EO or EE3ME	15	10	10	12
	15	9	66	
Provera + EE3ME, 0.1 mg	20	6	20	Approx. 15
	10	10	0	
Norethynodrel	20	1	(100)	?? 15
	10	2	0	
17 α -methylallyl-19-nortestosterone	40	2	0	0
	30	2	0	
	20	2	0	

response relationship exists for norethisterone (Primolut N), norethisterone acetate and Enavid (norethynodrel + ethynodiol-3-methyl ether [EE3ME]), the 50% effective doses of which are approximately 4.25, 10.25 and 5 mg respectively (Table I). With dimethisterone (Secrosteron) no positive responses have been obtained with doses up to 80 mg. Similar negative results have been obtained with 17 α -methyl-19-nortestosterone with doses up to 40 mg. A few tests with 21-methyl norethisterone have shown that the 50% effective dose is certainly greater than 15 mg and probably greater than 30 mg. With 6-methyl-17-acetoxy progesterone (Provera), Greenblatt (unpublished data, 1959) has found negative responses with doses up to 30 mg but we have found that the addition of EE3ME, 0.1 mg daily, gives a 50% effective dose of approximately 15 mg. A few observations on norethynodrel suggest that the 50% effective dose for this will be about 15 mg—as compared with 5 mg for Enavid. The addition of oestrogen supplements to dimethisterone has been ineffectual, no positive responses having been obtained with doses of the latter up to 40 mg daily. The reason for the apparent increase in effectiveness of some progestogens, but not others, when small amounts of oestrogen are added is obscure.

Withdrawal bleeding.—Patients with long-standing secondary amenorrhoea were employed in this trial and were instructed to take progestogen tablets for five days. If a withdrawal bleeding began within the next ten days, they were asked to begin a second course, a month after the first, but at half the dose. If there was no bleeding within ten days of completing the first course, a second course was begun at double the dose. This process of doubling or halving was continued until the maximally ineffective and minimally effective doses were established. Data have been accumulated on norethisterone, norethisterone acetate, Enavid, dimethisterone, 21-methyl norethisterone, 17 α -methyl-19-nortestosterone and Provera. Meaningful dose-response relationships have not been found, indicating that many uncontrolled factors, other than dose of treatment, influence the result and it is concluded that this criterion is not a suitable one for comparison of potency ratios of progestogens (Table II).

Effects on vaginal smears.—45 series of vaginal smears, in patients with secondary amenorrhoea given progestogens, have been studied. In 23, treatment produced no change. With norethisterone, 6 series showed progestational and 2 showed oestrogenic changes while 5 showed no change. With norethisterone acetate, 4 series showed progestational and 3 oestrogenic changes while 12 showed no change. With Enavid all

TABLE II.—WITHDRAWAL BLEEDING

Drug	Daily dose, mg	No. of observations	% of positive responses
Norethisterone	20	6	66
	10	13	92
	5	15	66
	2.5	9	78
	10-30	18	100
Norethisterone acetate	10	5	80
	5	6	60
	4	5	40
	2	10	66
	1	15	64
Enavid + EO, 0.01 mg	0.5	5	80
	20	2	(50)
	10	8	50
	5	3	(100)
	2.5	1	(100)
Enavid	10	11	100
	40	2	0
	20	5	40
	10	4	50
21-methyl norethisterone	5	2	0
	30	1	(100)
	15	4	50
17 α -methyl-19-nortestosterone	7.5	1	(100)
	40	2	0
	20	3	33
Provera	10	2	0
	5	2	100

series showed some changes—6 progestational and 2 oestrogenic. With dimethisterone, none of 6 series showed any change. It is concluded that vaginal smear changes are not likely to provide a suitable criterion for the comparison of progestational activity.

Summary.—Of a number of criteria considered for the determination of the relative potency of progestogens in the human, postponement of menstruation in normal women given the drug for twenty days from the twentieth day of the cycle seems most likely to provide data on which statistical evaluation of potency ratios may be made. The 50% effective doses for some progestogens are as follows: norethisterone (Primolut N) 4.25 mg, norethisterone acetate 10.25 mg, norethynodrel + ethynodiol-3-methyl ether (Enavid) 5 mg, dimethisterone (Secrosteron) more than 80 mg. Observations on withdrawal bleeding and vaginal smear changes in women with secondary amenorrhoea make it unlikely that these will provide suitable criteria for the comparison of progestational activity.

Grateful acknowledgment is made to Messrs. British Drug Houses, Ltd., Schering A. G. and Searle & Co. Ltd. for providing the steroids used in this study.

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■ (List of other papers read will be published later.)

Primo ^Nut ^N the potent oral progestogen

19-Nor-*o*-*h*ydro-*o*-*h*estosterone

Powerful oral progestogen
... wt. for wt. at least as potent
as intramuscular progesterone

Proc. Roy. Soc. Med., Vol. 51,
No. 7, July 1958, p. 520
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President—DAVID TREVOR, M.S.

Meeting
November 6, 1959

Ununited Fracture of the Neck of Femur

By Professor R. MERLE D'AUBIGNÉ
Paris

NON-UNION (or pseudarthrosis) of the fractured femoral neck can be divided into three main groups:

(1) Those cases in which the fragments are normal, provided with an adequate blood supply. In these, non-union is due to absence of treatment, lack of reduction or lack of immobilization. Union can be obtained by simple means, i.e. adequate reduction and fixation of the fracture even if this has been delayed for six months or more.

(2) Those cases where the proximal fragment is deprived by the fracture of its blood supply. Bony union can be obtained by adequate reduction and fixation but the necrotic femoral head is liable to collapse after weight-bearing even after bony union of the fracture has been obtained. This may occur many months or even years after union of the fracture.

(3) Cases where a second fracture occurs after the onset of the aseptic necrosis of the femoral head. For example, a trochanteric fracture united after nailing but one year later a spontaneous subcapital fracture occurred. This second fracture occurred when the line of new blood vessels to the necrotic proximal fragment had reached the fragile subcapital region. Similarly on careful examination some radiographs of cases of non-union with displacement after treatment by nailing or screwing may show that the ununited fracture is proximal to the original one. Here one may be certain that the femoral head is necrotic and the pseudarthrosis a severe one.

About half of all the fractures of the femoral neck treated by the old conservative method of plaster immobilization resulted in bony union after accurate reduction; the remainder ended in fibrous union, sometimes firm, or non-union.

Operative fixation of this fracture gives successful bony union in about 55% within 3 months with a normal hip. About 20% result in delayed union often with shortening of the femoral neck and late pain due to deformation of the femoral head. In about 10% early displacement of the fracture occurs and in 15% late displacement occurs, generally due to a

pathological fracture through the line of "creeping substitution." These last two groups of non-union are the most difficult to treat.

It is possible that causes other than faulty treatment or aseptic necrosis are responsible for non-union in fractures of the femoral neck. Harrold, 1959, has shown the presence of an anticoagulant substance in synovial fluid which prevents the formation of blood clot necessary for the development of callus.

Most writers consider that lack of adequate blood supply to the femoral head is the main cause of non-union in fractures of the neck of that bone. They believe that this is the chief factor influencing prognosis and the choice of operative procedure. On this assumption we have treated some cases with preservation of the femoral head and others by its removal. Results show that we have preserved some necrotic heads; possibly we have removed some living ones.

REVIEW OF CASES OF NON-UNION OF FEMORAL NECK FRACTURES

306 cases have been reviewed, which include all those treated in the past fifteen years. Those few patients treated by Whitman's operation have been omitted. Other patients could not be traced or died shortly after operation. Excluding the above there are 226 cases available for study. The treatment for all patients was operative.

In 72 patients the femoral head was preserved; of these 18 were nailed, in 41 an osteotomy was carried out and in 13 an intra-articular operation.

In 134 patients the femoral head was removed and replaced by a prosthesis. In 20 an arthrodesis was performed.

Total	Nailing	Osteotomy	Intra-articular operation	Prosthesis	Arthrodesis
226	18	41	13	134	20

Nailing.—This can only be done after relatively recent injury where good reduction of the fracture can be obtained. In all of these reduction and fixation by a Smith-Petersen nail under radiographic control was the method used. In 8 patients a bone graft was also used.

These were all cases in which there had been no previous operative treatment and where it was considered that the femoral head was alive.

In 2 patients, where a bone graft was used with a nail, redisplacement occurred with fracture of the graft. In all other cases bony union was obtained. However, in 7 patients necrosis of the femoral head occurred, resulting in pain and deterioration of function. Addition of a bone graft to the nailing had no beneficial influence on the result.

Of these 18 patients with an ununited fracture four to thirteen months old, 11 had a practically normal hip when reviewed two to sixteen years after operation.

TABLE II				
	No.	Bony union	Necrosis	Good result
Nail	10	10	7	11
Nail + graft	8	6 }		

Osteotomy.—Where there is fibrous union between the cervical part and a displaced femoral head this can be converted into bony union by an osteotomy with abduction and medial displacement of the shaft. This gives support to the head and transforms the shearing forces into compression.

The technique used during the years 1940-44 was that of Putti's intertrochanteric type but with fixation by a nail and wire. As redisplacement of the femoral head sometimes occurred we changed our technique to fixation of the femoral head and osteotomy by a nail plate of the MacLaughlin type.

The failures are due to: (1) Early redisplacement of the femoral head, possibly due to insufficient abduction of the femoral shaft. (2) Late redisplacement or, more accurately, late collapse of the femoral head. This was the most common cause of failure. The femoral head kept its normal shape as long as it was ununited and therefore non-weight-bearing. When as a result of the osteotomy the femoral head becomes weight-bearing, collapse may occur, particularly if at that time new blood vessels are growing in from the femoral neck.

We considered that these failures might be due to fibrocartilage having developed over the fracture surfaces—thus obstructing the growth of blood vessels from the femoral neck into the head.

It seemed to us more logical to open the hip-joint, freshen the fractured surface of the femoral head and excise the upper surface of the femoral neck, so getting good stable contact. By this means there would be more likelihood of revascularisation of the femoral head across the osteotomy site, with bony union. This operation was designed by us at the same time as Luck in the United States (Luck, 1938).

16 patients were operated on by this technique. 12 have been followed up for two to seventeen years. Of these 12, 5 results were good, i.e. solid union, revascularization of the femoral head and a practically normal hip. In 7 cases there was collapse of the femoral head with recurrence of pain and limp. 4 of these patients were subjected to further operation. The high percentage of avascular necrosis—higher than that of nailing or simple osteotomy—may probably be explained by the intra-articular approach and manipulation of the femoral head. This would tend to destroy the few remaining patent blood vessels.

It is probably better to remove a large part of the bone of the femoral head (Brackett, 1927)—or all of it—leaving a cartilaginous shell (Moore, 1948) and insert the freshened stump of the neck into the cavity thus formed. One patient—a girl of 14 years with non-union after 2 bone grafting operations—was treated by Brackett's method. This gave an excellent result.

TABLE III					
	Patients	Followed up	Solid union	Necrosis	2nd operation
Luck	16	12	5	7	4
Brackett	1	1	1		

Of the 72 patients operated on where the femoral head was preserved there were 27 failures—a failure rate of 37.5%. The majority of these were due to aseptic necrosis of the femoral head.

The high percentage of failures following operations retaining the femoral head led many surgeons to devise other operations in which the necrotic or partially necrotic femoral head was removed.

They have advocated the insertion of a prosthesis or an arthrodesis of the hip. 15 patients were treated by various types of resection of the femoral head—these included Colonna's method and Wilson's modification of this procedure covering the greater trochanter by a metal cup (Colonna, 1935; Wilson, 1947).

Most of these hips became relatively painless; few are stable. Only a small percentage can be classified as good and such results were only obtained after months and sometimes years of post-operative treatment.

We consider that these procedures belong to the past and that much better results can be obtained by the use of a prosthesis in spite of their disadvantages and possible late complications.

We consider, however, that the Judet's type of prosthesis also belongs to the past. Where there is non-union with a short neck stump this prosthesis does not restore the length of the femoral neck. Too great pressure per surface

unit of the neck stump causes absorption of bone and loosening of the prosthesis, with subsequent pain and impairment of function.

Judet's prosthesis was used in 70 patients before 1951. 54 have been followed for three to eleven years (average five and a half years). The results were: Excellent 13%; good 30%; fair 18%; poor 39%. Thus more than 50% are failures. 7 out of 22 patients followed up for more than five years certainly can be classified as excellent results but 9 patients had to undergo a second operation—16.6%.

Since 1950 we have discontinued the use of the cervical prosthesis (Judet type) and have used a cervico-capital acrylic prosthesis with a long intramedullary stainless steel stem. This type of prosthesis gives wider distribution on to the sound bone of the lesser trochanter and base of the femoral neck. However, as all but the intramedullary stem is made of acrylic there is still the risk of the absorption of small particles of this material into the surrounding tissues.

Acrylic has certain advantages over metal as it is softer, cheaper and easier to work. It is interesting to compare the results of this cervico-capital prosthesis with those of Judet's. This comparison might provide evidence as to the cause of bone absorption around the prosthesis—is it due to the pressure of a foreign body, whatever the material, on the bones?

107 patients have had this cervico-capital prosthesis inserted for non-union or necrosis of the femoral head. 4 died during the first year, 17 were lost sight of and 3 cannot properly be included—1 because of a hemiplegia and 2 because of other lower limb fractures. 3 cases of post-operative infection have also been excluded.

There thus remain 80 patients followed up from two to nine years. There has been no fracture of the prosthesis but 9 fractures of the greater trochanter and 2 dislocations, of which one was successfully reduced. The late results are as follows: Excellent 29; good 35; fair 7; poor 9.

This gives 80% satisfactory results and 20% unsatisfactory ones. However, 8 of these arthroplasties were done on failed "cephalic" arthroplasties. If we confine ourselves to primary arthroplasties followed up for four years or more, the comparison will be more significant. This gives a figure of 75% excellent and good arthroplasties where the cervico-capital prosthesis was used against 35% with the old original type of cervical prosthesis.

There is, however, still some doubt as to the future of these patients. Careful examination of subsequent radiographs have shown in some cases bone absorption around the prosthesis,

cysts in the acetabulum and abnormal bone sclerosis. Out of 59 primary arthroplasties these changes occurred in 7 (12%) and were progressive. None was seen before two years, between two and four years they were found in 17% of the patients, between four and six years in 22% and after six years in 38%. However, amongst 13 patients with radiological deterioration 6 still had a good, painless hip.

From the above figures it is evident that the cervico-capital prosthesis, due to more even distribution of pressure on the bone, gives better and more lasting results than those obtained from the early Judet's type. There may, however, still be the risk of clinical and radiological deterioration in all these patients where plastic material is used in the prosthesis. We are therefore now using Vitallium or titanium prostheses of the Austin Moore type more frequently.

17 such prostheses have been used by us in the last two years. So far the results have been satisfactory but we wonder if this hard metallic material will not result in undue wear on the acetabulum.

The use of prosthetic femoral heads is a great advantage in the treatment of ununited fractures of the femoral neck, particularly where there is extensive necrosis, enabling many patients to lead a normal life unobtainable by other older methods. They are invaluable in elderly people who lead a quiet life and this is the chief age group with ununited fracture of the femoral neck.

In younger patients who will lead a more active life, arthrodesis when the femoral head is necrotic is a most valuable operation, but to obtain bony fusion is not easy. This operation was carried out in 20 patients—3 were failed arthroplasties, 3 failed osteotomies and 1 had been infected at a previous operation. Of these 20, bony fusion was obtained in 15 but 17 had excellent or good results, including 3 where the fusion was doubtful.

3 patients required two operations to obtain bony ankylosis.

In these arthrodeses the procedure followed was a postero-lateral incision, removal of the femoral head and freshening up of the acetabulum, femoral neck stump and greater trochanter. The tip of the trochanter was inserted into the upper part of the acetabulum and fixed by a nail or two screws. The remainder of the acetabular cavity was filled with chips obtained from the femoral head. Finally a tibial graft extending from the back of the greater trochanter to the ilium was fixed by screws. In 2 cases where there was no femoral neck stump a subtrochanteric osteotomy was also carried out, in

I at the same operation and in 1 as a second stage. The position chosen was 20-degree flexion, neutral rotation and slight adduction, the last named being most important to avoid post-operative genu valgum.

Finally we consider that there are three operations from which to choose: (1) Osteotomy with nail plate, (2) cervico-capital prosthesis, preferably all metal, (3) arthrodesis.

Theoretically osteotomy is the best when the femoral head is alive; when it is necrotic a prosthesis should be used in old patients and, in the young, arthrodesis.

How can we determine whether the femoral head is alive? X-ray appearances can be misleading. Necrosis is probably present when redisplacement occurs after a correctly nailed or screwed fracture; it is certainly present when the line of pseudarthrosis (non-union) is proximal to the original fracture line. The femoral head may be alive when the non-union is due to non-reduction or insufficient fixation of the fracture.

Investigation by radio-isotopes, as described by Tucker (1950), Boyd and others, is still in the experimental state. Hulth (1958) has shown the possibility of demonstrating the vascularity of the femoral head by phlebography. We are investigating this method but have had too few cases to come to any conclusion.

As it is impossible to be sure whether a femoral head is alive in an ununited fracture, we carry out the following procedures:

	Femoral head alive	Femoral head doubtful	Femoral head necrotic
Patient with more than ten years active walking life	Osteotomy	Osteotomy	Arthrodesis
Patient with less than ten years active walking life	Osteotomy	Prosthesis	Prosthesis
Elderly patient	Prosthesis	Prosthesis	Prosthesis

If late complications due to necrosis of the femoral head should occur after an osteotomy an arthrodesis or insertion of a prosthesis can always be carried out.

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Meeting
December 1, 1959

The Problem of Byron's Lameness

By DENIS BROWNE, F.R.C.S.

London

BYRON, quite apart from his poetry, was an important figure in the history of thought. It is significant that Bertrand Russell, in his History of Western Philosophy, devotes a whole chapter to the influence of his conception of man engaged in a tragic and romantic war against the Universe.

One of the main causes of this attitude was his bitter resentment of the fate that, in spite of all his brains and beauty, made him a cripple. It is difficult for anyone interested in the various forms of crippling not to be fascinated by the problem of what caused Byron's lameness; that question on which so much ink has been spilt, so many inaccurate statements confidently made, and a considerable number of lies told.

An analysis of all the evidence would do little beyond quite unnecessarily establishing the unreliability of the human mind; but there are certain undeniable facts. The trouble was con-

fined to the right leg; the balance of evidence is overwhelmingly in favour of this. It was a congenital deformity, and at the birth the great John Hunter was called in to make, as one might expect, a sensible remark—about the only one to be found on the subject: "It will do very well in time." It did do well, to the extent of carrying Byron through a career full of physical as well as mental accomplishment.

These facts dispose completely of the suggestion that Byron was spastic, a surprisingly popular notion: spasticity is not a deformity, and slight degrees are never, even now, diagnosed at birth.

Then there is the definite statement, backed up by a woodcut in the *Lancet*, made by a contemporary surgeon, Sheldrake (1827-28), that Byron had an ordinary club-foot. Apart from the fact that this alleged picture of a cast of Byron's foot shows the left one (Cameron, 1923), Sheldrake's

complete lack of trustworthiness, obvious enough to anyone who reads his self-advertising wordy articles, is shown by the existence of real casts of that deformity, though they are casts in leather, not plaster. They consist of two devices worn by Byron as he was approaching manhood: they are in the possession of Sir John Murray, the descendant of Byron's original publisher of the same name, and by his courtesy I have been allowed to have them photographed. This has been done before, but not in such a way as to bring out their true nature.

It is important to realize that none of the treatment, painful and embarrassing though it was, that Byron suffered as a boy could have had the slightest influence on his deformity. In early youth he underwent a version of that well-known aid to Scottish justice, the torture of the boot; and later on indignant practitioners complained that their walking splints had been thrown into ponds or were flapping loose in the breeze: we can all sympathize with them. But those who have struggled with congenital deformities of the feet will realize that none of this could have altered in any way their stubborn tendency to resume their original form (Little, 1928).

Consequently to elucidate the problem what we have to do is to find patients of the present day wearing similar devices, devices that do not aim at correcting a deformity but at disguising it. What had to be disguised was a grotesquely thin calf and a small foot, a failure of the region to form properly: a dysplasia and not a moulding deformity such as a club-foot. The present failure of my colleagues to recognize that feet can be moulded before birth as well as after-

wards (in the case of Chinese foot-binding) rather complicates my exposition, but I have said enough on that subject elsewhere.

The calf of the legging illustrated in Figs. 1 and 2 has thick padding which would give the effect of a normal calf inside the long trousers from which Byron refused to be parted in public, apparently even when swimming. The inner boot that surrounds the foot would fill up the lasts that are still in existence, and so make the two feet look alike in ordinary use.

The foot itself is not in the least like a club foot, so called because if untreated it contracts and turns upside down into a rounded club-like lump; it is a long narrow foot in slight metatarsal varus, that is, with a bend inwards towards the middle of its length (Figs. 3 and 4). Feet of this



FIG. 3.—View of sole of inner shoe, with alongside it a metatarsal varus foot of the type which would fit it.

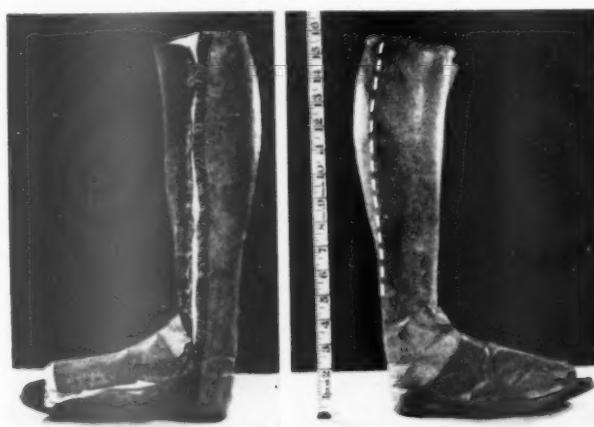


FIG. 1.—View of inner side of legging, to show lacing.



FIG. 2.—Outer side of legging, with extent of padding outlined by dotted line.



FIG. 4.—Outline of a true club foot superimposed on tracing of the foot in Fig. 3.



FIG. 5.—Untreated congenital dysplasia of left leg. The girl ordinarily wears a legging and inner shoe almost exactly like Lord Byron's to disguise the deformity.

dysplastic kind are always stiff, so there would be a lack of ankle movement, which would account for the sliding gait described by one of the few accurate observers.

Figs. 5 and 6 demonstrate a similar case illustrating the strange fact that these dysplasias of the limbs tend to occur in children who, apart from them, are above the average physically and mentally.

If I am right about this problem one important



FIG. 6.—The case shown in Fig. 5 at 6 months of age, showing the congenital nature of the deformity.

point is established that may make Byron rest easier in his grave; no form of treatment known now or likely to be invented in the future could have made any real improvement to his violently resented deformity.

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Some Thoughts on the Antibiotic Therapy of Orthopædic Tuberculosis [Summary]

By H. R. W. LUNT, M.Ch.Orthop.
Derby

(1) 100 cases of bone tuberculosis treated by antibiotic therapy with or without surgical debridement were reviewed.

(2) The importance of a bactericidal combination and concentration of antibiotic in the serum was stressed and the improved clinical response to high dosage indicated.

(3) 20 mg/kg of body weight of both Dimycin and isoniazid was advocated as necessary to achieve a bactericidal serum level, with 100 mg/kg of body weight of PAS essential to inhibit in-

activation of isoniazid in the patient who acetylates I.N.H. rapidly.

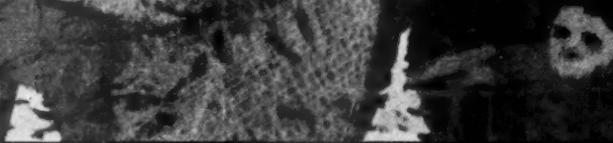
(4) Reference to the work of Mackaness and Smith (1952, 1953) and to that of Middlebrook *et al.* (1959) confirmed the need for this level of medication.

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The following films were shown:

The Operative Technique for Temporomandibular Joint Ankylosis.—Mr. M. S. HOROWITZ.
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Meeting
February 19, 1960

The Role of the World Health Organization in Epidemiology [Abridged]

By J. D. COTTRELL, M.R.C.P., D.P.H.¹

Copenhagen

Introductory

THE World Health Organization (WHO) is a specialized agency of the United Nations. Its work is directed and approved by the World Health Assembly, composed of delegates of the governments of the 90 Member States, and by an Executive Board of 18, nominated by, but not representing, governments.

For greater efficiency, 6 regional offices have been established; the United Kingdom is a member of the European Region. The 1960 budget is approximately 17 million dollars, 1.2 million being devoted to the European Region. Besides the contributions from Member States, other funds are received from the United Nations Expanded Programme of Technical Assistance, from the United Nations Children's Fund (UNICEF), and from the Malaria Eradication Special Account.

WHO and Research

International collaboration is desirable in many research projects, e.g.:

(1) Demographic studies, genetic descriptions of populations, disease incidence and prevalence studies, identification of environmental factors causing disease and similar problems of regional or global significance.

(2) Communicable diseases of widespread or world-wide distribution.

(3) Unexplained variations in the incidence and prevalence of disease and in health in widely different environments and under various economic conditions.

(4) Research on rare conditions which require pooling of information to collect together a significant amount of data, the study of which may have wider applications.

(5) Projects requiring special skills in which progress is being delayed because of lack of intercommunication between research workers.

Classical epidemiological techniques can be applied to many of these problems.

WHO does not normally undertake research itself but seeks to supplement national research efforts. This it does by: (1) Establishment of reference centres, standardization of methods, reagents, and nomenclature, and provision of other similar services. (2) Training research workers. (3) Improving intercommunication between research workers. (4) Supporting research by provision of personnel, equipment and grants. (5) Assistance in planning research institutions and programmes.

Valuable results have been obtained by encouraging all staff members, including field staff, to incorporate research work wherever possible in their activities.

Epidemiology

The statistical and epidemiological work of WHO may be considered under four headings:

(1) *General activities*.—The pattern followed in WHO's epidemiological work is the same as in other fields—the convening of expert committees to study the problem, the holding of seminars to spread information, *ad hoc* assistance in response to specific requests (WHO only intervenes by invitation of the government concerned) and training in scientific methods by the provision of fellowships and courses.

A task inherited from pre-existing organizations and a prime duty of WHO is to ensure that work carried out in different countries and institutions is comparable. One means to this end has been the publication of the "Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death" (WHO, 1957a). These standards must not only be issued but people have to be induced to use them; even within the United Kingdom the international form of medical certificate of cause of death is not universally used.

Continuity in the study of these problems is provided by a series of meetings of expert committees on health statistics, by the establishment of a WHO Centre for Classification of Diseases

¹World Health Organization Regional Office for Europe, Copenhagen, Denmark.

in London to which all countries can turn for advice, and by the support given to national committees on vital and health statistics in Member States. It is hoped that eventually mortality reports from different Member States will be comparable; this is a long-term project and comparisons made to-day of the mortality experience of different countries show widely differing standards.

These difficulties apply equally to morbidity figures. WHO tries to establish standardization of procedures and nomenclature in many fields as an essential prelude for comparable epidemiological studies in different countries or even different areas in a single country. It is often found that wide variations can exist between communities in the same country which at first sight might be thought comparable. These local differences are a challenge to epidemiologists and a forewarning of difficulties likely to arise in international studies.

In their sixth report the Expert Committee on Health Statistics (WHO, 1959b) laid down concepts, definitions and terminology for measurement of morbidity and considered their applicability to special studies. The same Committee made recommendations for studying the epidemiology of cancer. Similarly a Study Group on the Classification of Atherosclerotic Lesions (WHO, 1958) attempted to formulate a universally acceptable definition of atherosclerosis and laid down methods of grading and recording the lesions in this disease. The Expert Committee on Cardiovascular Disease and Hypertension in its first report (WHO, 1959a) suggested diagnostic criteria and a system of classification. A final example is provided by the eighth report of the Expert Committee on Mental Health (WHO, 1960) which deals with the epidemiology of mental disorders.

WHO runs an epidemiological intelligence service; governments are required to inform the Organization about quarantinable diseases occurring within their territories. This information is collated and distributed by wireless, telegram and airmail, and is further reported in the *Weekly Epidemiological Record*. Other mortality and morbidity figures are published monthly in the *Epidemiological and Vital Statistics Report*. Information on non-quarantinable diseases, e.g. influenza and poliomyelitis, is disseminated whenever their prevalence justifies this. In this connexion WHO collected and issued information on the spread of Asian influenza during the 1957 epidemic. A network of regional and national influenza centres has been set up in more than forty countries and they are linked either with the World Influenza Centre in London or with a similar Influenza Centre for

the Americas in Alabama. This system of laboratories is being extended to cover many other diseases of international importance, including intestinal and streptococcal infections and brucellosis. Reference centres for cancer, atherosclerosis and other diseases are being planned.

(2) *Special studies*.—WHO has initiated a series of special studies on world-wide or regional diseases. The first group is exemplified by the studies of Pollitzer on cholera and on plague which have been published in the *Bulletin of the World Health Organization*, and subsequently also as WHO monographs (Pollitzer, 1954, 1959). An example of work done on a regional basis is the group of surveys carried out to detect bilharziasis in a number of countries in south-west Asia and parts of Africa.

A special venture in this field, the Group Report on "Accidents in Childhood; Facts as a basis for Prevention" (WHO, 1957b), was a first major attempt to examine the epidemiology of accidents from an international point of view. The Group collected and reviewed many epidemiological studies and tabulated this data. It studied the available mortality figures and stressed the need for morbidity figures as well, including figures of "near accidents," so that information on accident risks, probabilities, rates and so on could be deduced. It enumerated the principles for designing sample surveys of the population and a plan for collecting information on accidents which would serve as a basis for accident prevention.

(3) *Epidemiological work in disease control activities*.—Large-scale programmes have been organized in many countries, often in collaboration with UNICEF, to assist governments in the control of communicable diseases such as malaria, tuberculosis, yaws and trachoma. Much research has been carried out in connexion with these projects and considerable epidemiological information obtained.

In the case of tuberculosis, this research was furthered by the establishment in 1949 of a special Tuberculosis Research Office (T.R.O.) and the examples given below are by-products of mass BCG vaccination projects.

By mid-1959 over 265 million tuberculin tests had been carried out all over the world under the auspices first of the International Tuberculosis Campaign and later of WHO and UNICEF.

The great majority were intradermal Mantoux tests made with a measured dose of standardized Danish tuberculin. The largest transverse diameter of skin induration was measured with a ruler after three to four days by trained staff.

Routine field work was directed and evaluated by the T.R.O. and by specially trained field assessment teams. While these millions of tests

were probably not all accurately standardized, at any rate by following a standard routine their performance could be checked by the assessment teams and the causes of anomalies could be investigated, including the extent of "observer error". These studies would have been impossible if the different tests in common use had been used indiscriminately.

Certain important practical facts emerged concerning the use of tuberculin in the Mantoux test. Not only do different batches of purified protein derivative (PPD) give somewhat different results, but any particular tuberculin will lose its potency if exposed to heat or sunlight or even if kept in incompletely filled bottles when it is adsorbed to the container to a varying degree (Guld *et al.*, 1955; Magnus *et al.*, 1956).

The main achievement was obtaining comparable information on tuberculin sensitivity on a world-wide scale, something which had never been done before. This included a large amount of new information about "low grade" tuberculin sensitivity, first described by Carroll Palmer and his associates in the 1940s and recently summarized by Edwards *et al.* (1959). The appointment of Palmer to the T.R.O. afforded an opportunity to study this phenomenon intensively on a global scale.

Palmer *et al.* (1959) have produced strong evidence that in U.S.A. low-grade sensitivity is due to infection with mycobacteria other than *M. tuberculosis*. Whatever the cause, its presence greatly complicates a BCG vaccination campaign. If histograms are constructed, grouping individuals according to size of reaction, in a country like Mexico where low-grade reactions are uncommon, there are two clearly defined groups: non-reactors and strong reactors. The reactions in the latter group are comparable in size with the reactions seen in known cases of tuberculosis (WHO/T.R.O., 1955). In a country like the Sudan where low-grade sensitivity is common, there is no clear distinction between these two groups and it becomes impossible, by means of a simple Mantoux test, to separate clearly the non-infected children who should be vaccinated from those infected who should not.

It has been shown in the United Kingdom that low-grade tuberculin sensitivity may be associated with some degree of immunity against tuberculous disease. It is uncertain to what extent it affects the development of immunity following BCG vaccination (Medical Research Council, 1959).

In 1954 the Government of the Sudan asked WHO to make a tuberculin survey to determine whether a mass BCG campaign was needed and, if so, how it could best be carried out. The

survey, which was a joint effort by WHO UNICEF and the Government was made over a twelve-month period by a specially trained team under the technical direction of the T.R.O.

281 groups selected at random, scattered throughout the country, were examined, including the population of 47 villages, children from 192 schools and members of urban groups, such as police, students, &c. The testing in schools and groups was relatively complete: on an average 91% of the persons in these groups were tuberculin tested and the test was read. Little is known about the village populations but in the few instances where the size of the population could be estimated about 70% were tested. Standard Mantoux techniques were used, giving 5 I.U. using a Danish PPD. In the survey 56,000 people were tested and 26,000 were given BCG. The total population of the Sudan is estimated at 10 million.

Owing to the prevalence of low-grade sensitivity it proved difficult to decide the size of reaction separating infected from non-infected children. It is known that in Sudan, as elsewhere in the world, the sizes of Mantoux reactions in tuberculous patients are symmetrically distributed round a maximum of 16-18 mm (WHO/T.R.O., 1955). On this basis an attempt can be made to estimate the number of children infected with tuberculosis. In deciding which children to vaccinate, it is necessary to weigh the importance of vaccinating as many uninfected children as possible against the desirability of keeping vaccination of the infected to a minimum and eventually an arbitrary decision must be made.

The Government was advised that the prevalence of tuberculosis was high, that a general BCG campaign was justified and that the "negative-positive" level was difficult to estimate but for the purposes of a campaign 7 mm might be appropriate. Incidentally, 5,000 additional tests were carried out with histoplasmin; in two areas only was a significant number of positive tests found so this infection was obviously rare.

(4) *Co-ordinated international research.*—Consideration is currently being given to the co-ordination of studies undertaken by a number of research groups on the outcome of pregnancies in the United Kingdom and other European countries; it is probable that this study will be extended to other regions. In 1953 and in 1956 the WHO Regional Office for Europe convened meetings to consider aspects of perinatal mortality and morbidity. The 1956 meeting laid down a series of agreed definitions and a scheme for the studies to be used by the group. This included obstetrical, clinical, pathological and some social data, but since events during the perinatal period are frequently caused by

environmental factors occurring during the early period of gestation, the idea of an internationally co-ordinated prospective study arose. In 1958 contact was established with the National Institutes of Research in the United States which were planning a similar study. A WHO consultant visited a number of groups in the European Region and also saw the work in the United States, and as a result a new meeting was held in December 1959 in Copenhagen, attended by representatives of groups already working in this field who will probably take part in the co-ordinated studies.

The primary objective of the study is to record events during pregnancy and parturition and correlate these with defects in the foetus. It is clear that as defects are relatively infrequent a large number of pregnancies will have to be studied. It therefore seems to be a project well suited for international co-ordination.

Another series of studies is designed to investigate the differences in cardiovascular mortality reported by various European countries. There may be real differences in the amount of cardiovascular disease and of arteriosclerosis in the population and hence in the mortality from these diseases; on the other hand they may simply be due to discrepancies in terminology, in diagnostic customs or in coding procedures.

A consultant was appointed in August 1958 to investigate the second possibility, i.e. whether these differences are statistical artifacts. This study will be made at first in Denmark, England and Wales, Finland, France, the German Federal Republic and Scotland. These countries have been selected to cover a wide range of reported death rates from cardiovascular disease.

It was decided, to begin with, to compare coding practices in these countries using the method of coding in England and Wales as a standard and for this we are very grateful to the Registrar-General. The study is limited to death certificates of men and women between 45 and 64 years of age, but within that age range it covers all deaths. In this way it is hoped to include a maximum amount of cardiovascular disease, to get a complete picture of coding practices for all diagnoses and combinations of diagnoses and at the same time to avoid the complications of multiple causes of death in old people.

To get a clearer picture further complementary studies will be necessary, including a series of national studies on the reliability of diagnoses entered on death certificates. In particular it is proposed to carry out a series of morbidity and autopsy studies on the prevalence of cardiovascular disease in several countries in the

Region. For the autopsy studies there is a guide laid down by the Study Group on the Classification of Atherosclerotic Lesions, but there are two considerable difficulties in the way. The first is the problem of obtaining comparable autopsy samples in different countries. The second is to assess the observer error if the study is carried out by independent investigators, since if a single reference centre is designated there may be legal difficulties in sending relatively intact specimens from one country to another. It is hoped that these difficulties will be resolved during 1960. In the meantime WHO is proceeding with plans to establish a network of centres for pathological studies of atherosclerosis.

In this Regional Office we have been for some time studying a plan for a small series of national prevalence surveys to be co-ordinated by WHO. We hope that planning will be completed within the next few months and that a small pilot study will be started this year.

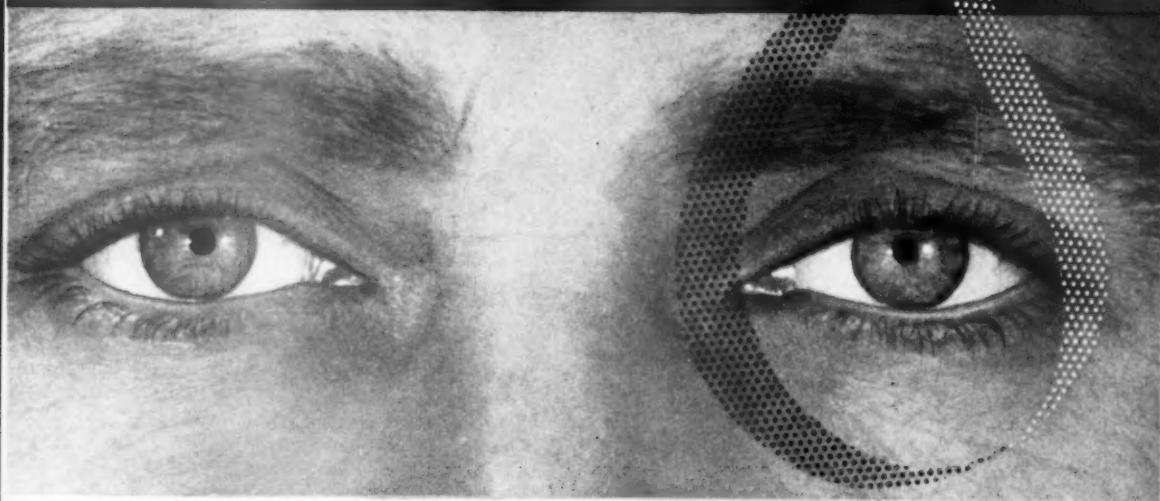
Another topic studied has been atmospheric pollution and WHO is now considering the reports of two consultants who have been visiting research centres in Europe and it seems likely that the Organization will be asked to assist in co-ordinating these studies as well.

Conclusion.—This survey of WHO's work in epidemiology has had to be both brief and selective. I hope that it will nevertheless serve as an introduction to the many important activities of WHO in this field.

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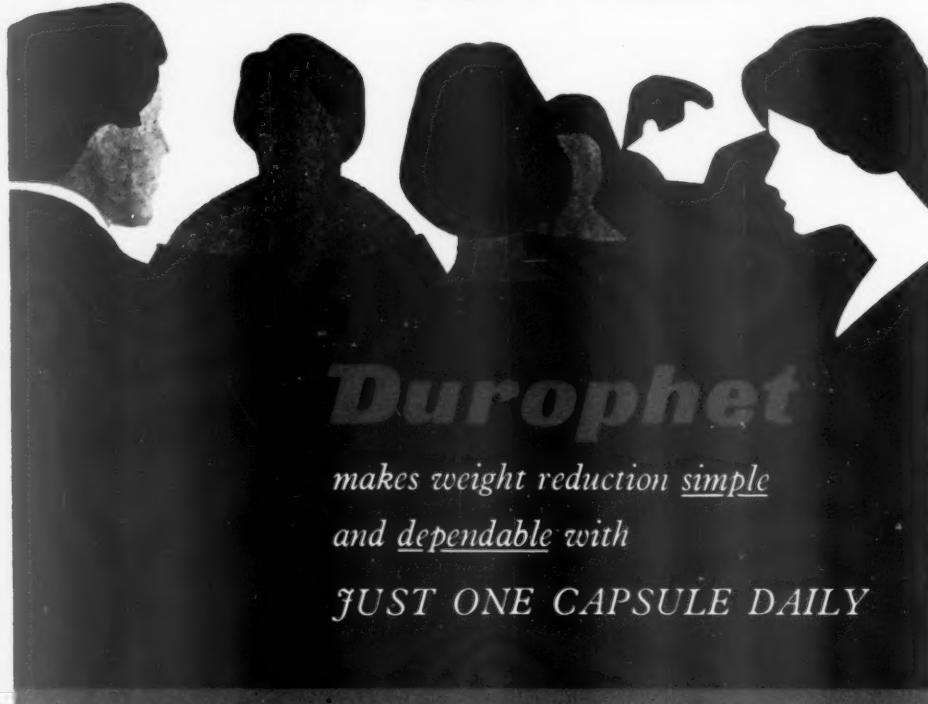
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President—DENIS BRINTON, D.M., F.R.C.P.

Meeting
February 4, 1960

DEVELOPMENT IN CONTRAST RADIOGRAPHY

What the Surgeon Needs to Know

By D. W. C. NORTHFIELD, M.S.

London

IT is unnecessary to emphasize that prior to radiological examination every detail of history and clinical examination must have been considered; not only in order to arrive at a diagnosis, but in order also to select as intelligently as possible the appropriate investigation. Now that radiology provides several techniques, one of which in any particular case may give the maximum information and be the least likely to give rise to dangerous complications, choice is a matter of importance. In some patients the question to be answered may be merely whether or not an expanding lesion is present; in other words a need to exclude that possibility. In such simple decisions air encephalography is usually employed, though if a vascular hamartoma is suspected, angiography will be necessary. Where the clinical diagnosis of tumour has been made, the investigation is chosen with a view to confirming its presence, and locating its situation and extent as accurately as possible. Twenty-five years ago that was about as far as radiology could take us; opinion upon the nature of the lesion was based—often insecurely—on the pattern of evolution of the illness, helped by the occasional presence of such coarse radiological features as hyperostosis, intracerebral calcification and the shape of an intraventricular shadow. The introduction of angiography has brought great improvement in the diagnosis of the pathology of the lesion, so that it is now the usual choice in order to demonstrate tumours of the cerebral hemispheres, and occasionally those in the posterior fossa. When the diagnosis suggests an intraventricular lesion, positive contrast media may give better identification than air replacement.

The value of angiography in demonstrating the pathological circulation in meningioma and in glioblastoma is now commonplace knowledge, though occasionally even the expert interpreter may have doubts. Filling of meningeal vessels may then be of decisive value. But the importance of bone changes should never be forgotten, and simple X-ray films should always be carefully scrutinized before other techniques are

employed. Previous craniotomies may lead to such distortion of the ventricles that the anticipated displacement by a recurrent tumour, or one not detected at the prior operation, may not occur.

Ocular palsy accompanied by trigeminal pain is highly suggestive of aneurysm, but there are alternative causes, and in these angiography may still be the method of choice. Atheroma of the internal carotid artery may calcify and mimic the appearance of aneurysm, and an angiogram not only excludes this lesion, but may reveal the filling defect caused by the atheromatous plaque. Tumours of the body of the sphenoid may be suspected if there is bone destruction, and demonstrated by their displacement of the carotid artery as it courses through the cavernous sinus.

Tumours within and above the sella turcica may give rise to a clear-cut clinical picture of endocrine failure and chiasmal compression. But it is of great practical value for the surgeon to know the extent of the destruction of the sella, how far the tumour extends above the sella and laterally, and its relationship to the third ventricle. Does the tumour merely displace it, does it invade it—in the sense that the tuber cinereum is directly involved (as in many cases of Rathke pouch tumour) or is the tumour primarily within the ventricle? Armed with this knowledge, the surgeon can decide whether a transphenoidal approach is best, or the classical transfrontal craniotomy; if the tumour is invading the tuber he will be content with a palliative partial removal. In cases of intraventricular tumour, he will more easily decide whether a transventricular exploration is advisable, a simple paracentesis of a cyst, or a ventriculo-cisternostomy. Air encephalography is a valuable help in these problems, provided the technique gives adequate filling of the basal cisterns, and sometimes is usefully combined with ventriculography. Where there is clinical evidence that the tumour has extended laterally—as in some cases of pituitary adenoma—angiography is justifiably carried out in addition.

The value of ventriculography in the definitive diagnosis of colloid cysts has been well under-

lined by Bull (1949), and is essential for all varieties of intraventricular tumours. The shape and site of the shadow and other features in the case may—as in colloid cysts, intraventricular meningioma and papilloma and pineal tumours—suggest the pathological diagnosis. In pineal tumours, the possibility of seeding should be borne in mind, for in the variety known as atypical teratoma, a deposit of tumour may occur in the region of the supra-optic recess giving rise to disturbances of tuberal function, and may be recognized by careful scrutiny of the shape of the ventricle.

It is in such cases that a positive contrast medium (e.g. Myodil) can give additional help by

providing finer detail. This is particularly so in lesions of the aqueduct, such as stenosis and tumour, which still further narrow or otherwise deform this already narrow passage. Tumours of the pons displace the aqueduct upwards, and the fourth ventricle backwards. A combination of air and Myodil, or air introduced above the lesion by ventricular puncture and below it by lumbar puncture may outline a fourth ventricle tumour clearly and safely. Finally, lesions straddling the foramen magnum (e.g. Arnold-Chiari malformations) may be revealed by a combination of air ventriculography and Myodil myelography. **REFERENCE**

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Technique of Positive Contrast Myelography

By G. F. SWANN, M.R.C.P.

London

Introduction.—Reid and Tutton (1953) made the following observations: "Although there has been no fundamental change in the radiographic methods, the modern trend is to a more meticulous technique. By this means only are comprehensive radiographs of first class quality obtained upon which deductions of value can be based."

This statement remains true today, and this paper adds very little to the basic technique and is concerned with refinements. The introduction of a new X-ray table constructed, among other things, to deal with the difficulties of myelography stimulated an effort to improve technique. This paper is based upon these efforts. When the author first started using this tilting table, he was more than surprised to learn that the senior X-ray engineer mainly concerned with the design of it had never seen a myelogram and was reluctant to modify his machine. The author insisted that he should witness such an examination and, having done so, he expressed willingness and enthusiasm to alter the apparatus.

This incident draws attention to the fact that a close liaison should exist between radiologist and manufacturer to increase the diagnostic efficiency of apparatus, and is probably best illustrated by the fact that the long and close association between the late Professor Erik Lysholm and manufacturer George Schönander resulted in the Swedish Skull Table, which has not been bettered and which has been plagiarized by manufacturers throughout the world.

Contrast medium.—As long ago as 1919, Dandy predicted the use of air to demonstrate spinal tumours. Air and water-soluble contrast media will not be discussed in this paper.

It should, however, be recorded that in 1922 Sicard and Forestier, using Lipiodol epidurally for the treatment of sciatica, noted that when some of this substance went into the subarachnoid space it was mobile, and they deliberately used it for myelography. Myodil is a synthetic refinement of this substance, for it is less viscous and does not cause a significant arachnoiditis. It was introduced in America for myelography by Steinhausen *et al.* in 1944. It is the most practical contrast medium to-day, and being heavier than cerebrospinal fluid it can be tilted through the subarachnoid space using the force of gravity.

The four principal aspects of the author's technique are: (1) An efficient harness. (2) The introduction of the contrast medium under fluoroscopic control. (3) The use of a lateral screening and radiographic unit. (4) The exact localization of spinal tumours by skin markers.

Harness.—An efficient harness is essential for myelography. It must be comfortable, give confidence and enable the patient to be tilted 75 to 80 degrees head or feet downwards. It must be easy to adjust and easy to disconnect rapidly in order to examine in the prone, supine or oblique position. Apologies must be made for these obvious statements, but often little regard is paid to the comfort of the patient who may slip out of an inadequate harness at a critical stage of the examination. It is important also for the radiologist to be comfortable so that he is able to control both the machine and the patient and perform his various manœuvres without effort. If he has to struggle with inadequate apparatus, he soon becomes exhausted and does not produce impeccable pictures.



FIG. 1A.

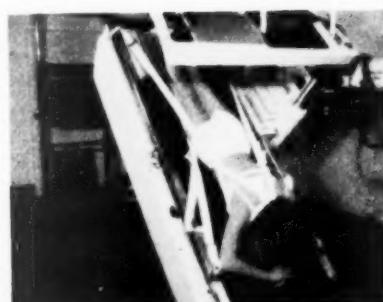


FIG. 1B.

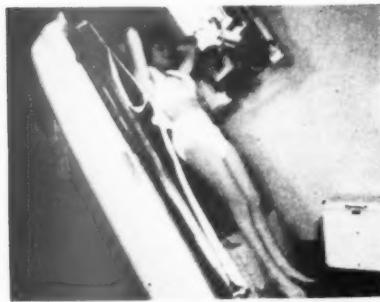


FIG. 1C.

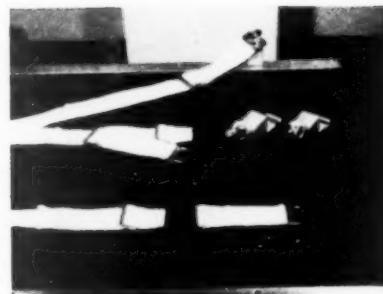


FIG. 1D.

FIG. 1.—Harness. A, The feet-down prone position. The patient sits in the harness taking the strain in the buttocks. The connexions for the shoulder have been clipped on to the table supports for the lower part of the harness, to be out of the way. B, The patient in the head-down position. Connexions for the upper and lower part of the harness are seen attached to the table supports. C, The feet-down supine position. The shoulder supports have been left slack and not clipped upwards to the opposite table supports. D, shows the individual components of the harness in detail. One table support is shown attached to the table top. Two others on the table top—one in the closed, the other in the open position.

The harness designed for use with this machine is made of nylon (Fig. 1) and was constructed by a maker of parachute harnesses. It is not at all bulky, and consists of separate upper and lower part; the upper part supports the patient in the head-down position and the lower part in the feet-down position. It is adjustable for different chest and pelvic measurements and its connexions to the table supports can be moved up and down the table. A quick-release mechanism enables the harness to be rapidly disconnected from the table-supports so that the patient may easily be moved. This is a comfortable harness. The author has tried it at 80 degrees head downwards for five minutes.

The Watson super tilt.—This new table (Fig. 2) has the great advantage that the under-couch X-ray tube is linked with another X-ray tube to take lateral pictures with a horizontal ray. The lateral screening unit supplied with this table has been modified and a film-carrier has been affixed to it so that rapid serial films can be

taken in a similar fashion to taking snap pictures of the duodenal cap during a barium meal examination. This table tilts 90 degrees each way at two speeds so that at the slower speed a very careful examination can be made.

In a conventional tilting table, the over-couch screen and under-couch X-ray tube are linked so that as the radiologist moves the screen the X-ray tube underneath the couch moves with it and is focused upon its centre. To take a lateral picture, however, another X-ray tube had to be brought into position from a distance, centred to where the Myodil was thought to be and the film fixed up against the patient, often only with sandbags. This was time-consuming, and often the Myodil had trickled away and therefore the films were inadequate. In this new table, the lateral X-ray tube is also linked with the under-couch X-ray tube and the over-couch screen; as the radiologist observes with the over-couch screen, the lateral X-ray tube will follow the Myodil as it is tilted through the lighter cerebro-

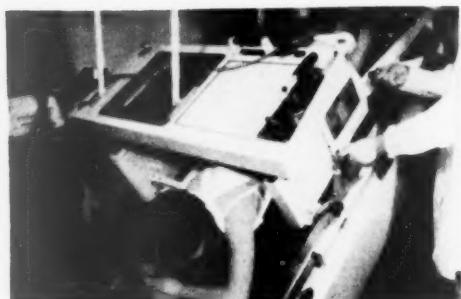


FIG. 2A.

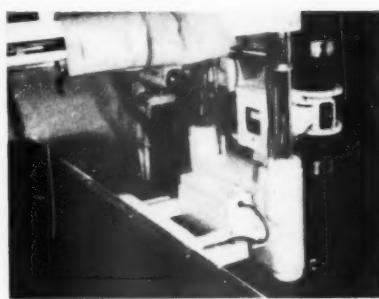


FIG. 2B.

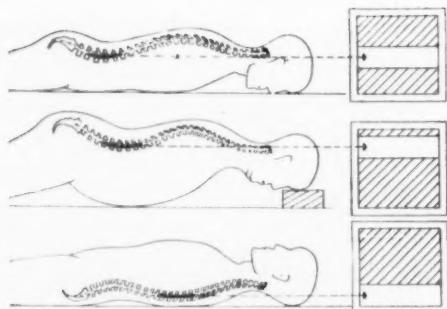
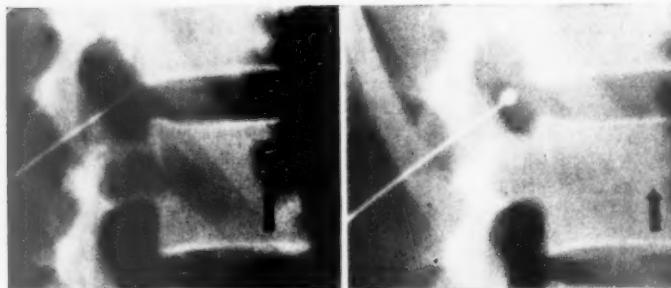
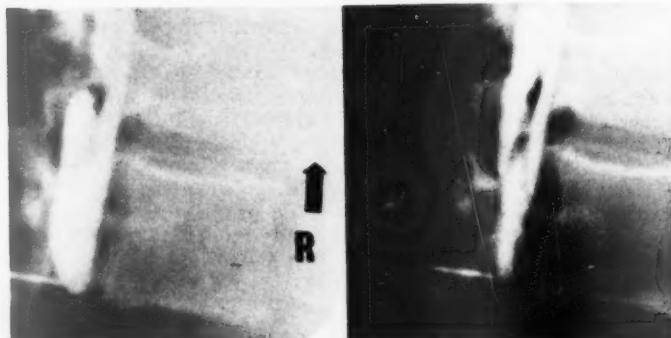


FIG. 2.—A, The radiologist about to take a lateral film with the new lateral screening device and radiographic unit. The under-couch tube cannot be seen. It is concealed under the table top. B, The lateral tube is here shown with the diaphragm in some detail. The connexion to the screening unit and the under-couch tube below are demonstrated. The height of the tube is also adjustable and can be pre-set for a fat or thin subject, thus giving additional range.

← FIG. 3.—This diagram shows how the height of the spinal theca from the table top can be accommodated by the leaves of the diaphragm.



← FIG. 4A.—Lateral radiograph showing the lumbar puncture needle in the spinal theca with 1 drop of Myodil being injected. It can be seen that the single drop of Myodil falls rapidly away from the needle point because the patient is tilted head down in the lateral position.



← FIG. 4B.—Shows the bulk of the 6 c.c. of contrast medium during injection falling rapidly away from the needle point, some of the roots of the cauda equina being demonstrated.



FIG. 5A.



FIG. 5B.



FIG. 5C.



FIG. 5D.—Supine.

FIG. 5.—Demonstrates the value of screening in the supine position. A, shows two lesions—a rounded filling defect at the disc space between L4-5; and another opposite the second sacral segment. B, lateral view. The upper arrow shows a small quantity of Myodil "capping" the small rounded lesion between L4-5; and the lower lesion partly surrounded and obliterating the rest of the sacral sac. C, oblique view showing both lesions. D, radiograph in the supine position showing an additional lesion at L2, which was not seen when the patient was screened prone.

spinal fluid. When he has positioned the Myodil satisfactorily in the antero-posterior view and has taken an antero-posterior radiograph the lateral X-ray tube is automatically in the correct position, and all the radiologist has to do is to pull the lateral screen opposite this and observe the Myodil and take lateral radiographs with a horizontal ray. This cuts down the time of the examination and reduces the incidence of inaccurate positioning of the Myodil in the lateral films. In addition, the lateral screening and radiographic unit has been attached to the

Potter-Bucky grid-carrier; it is counter-weighted and is therefore more manageable in the tilted positions and, because it is not attached to the table-top, is free from the harness connexions and can be moved into the desired position freely and rapidly. A special diaphragm is used with the lateral X-ray tube to produce a narrow strip of radiation which can be focused on the spinal theca. As the lateral position needs a larger amount of radiation to produce a good image, a sharper picture is obtained if scatter radiation is cut out by a narrow X-ray beam.

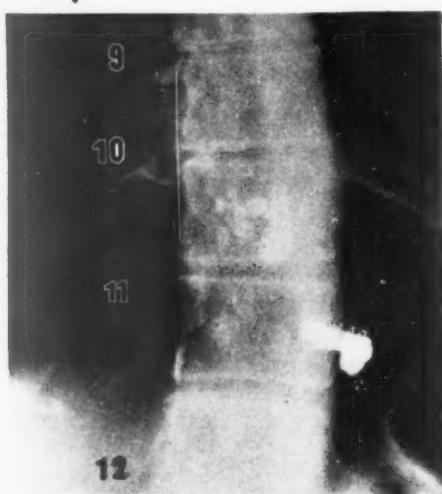


FIG. 6A.—Extension.



FIG. 6B.—Extension.

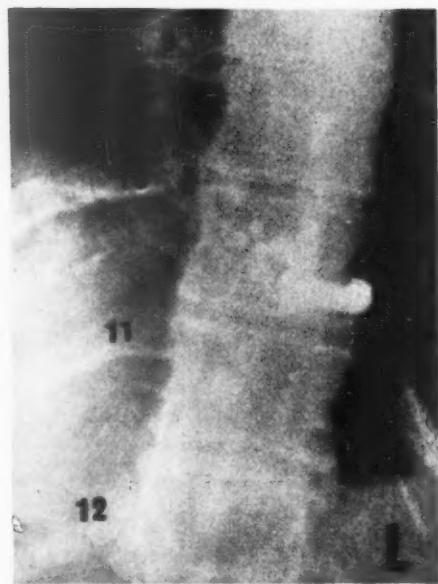


FIG. 6C.—Flexion.

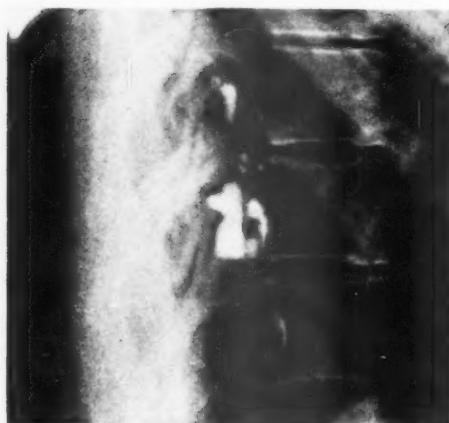


FIG. 6D.—Flexion.

FIG. 6.—A, a marker has been placed at the level of the block opposite the middle of the body of D11. B, lateral view. C, when the patient is flexed the marker has moved up almost to the mid-point of the body of D10. D, lateral view in the flexed position. These radiographs demonstrate the importance of allowing for the movement of the skin marker when the patient is put into the position favoured by the surgeon at laminectomy.

Technique

Introduction of Myodil.—The best way to introduce the Myodil into the subarachnoid space is under fluoroscopic control. The patient is put into the harness and turned into the lateral position. A short bevelled Greenfield

The diaphragm (Fig. 3) consists of an upper and lower leaf. These can pass each other and traverse the full extent of the aperture; thus a strip of radiation can be obtained at the top or bottom and in all intermediate positions of the aperture.

needle is introduced into the lower lumbar theca. The table is then tilted 15 to 20 degrees head down. The radiologist has been accommodating before he performs the lumbar puncture and without looking directly at and in the light of a 25-Watt lamp, removes his dark glasses and performs the lumbar puncture. The nurse or assistant connects the syringe of Myodil to the lumbar puncture needle with a polythene connexion. The radiologist screens and the nurse very gently injects one drop of Myodil. By this method a very high percentage of injections of Myodil into the subarachnoid space should be accomplished.

This technique has been evolved because in a significant proportion of cases where the Myodil is introduced blindly, subdural injection occurs, particularly if a lumbar puncture has been performed recently. The presence of subdural Myodil often precludes a satisfactory examination.

The patient lies in the head-down lateral position and one drop of Myodil is injected. If this is accurately placed in the subarachnoid space, it very rapidly falls towards the head under the influence of gravity (Fig. 4).

If the injection is in the subdural space, there is hardly any movement of the Myodil which spreads out as a blob or a streak.

Cisternal puncture is indicated if the patient is old or infirm or suffers from cardiorespiratory disease. The patient can then be tilted to the erect position and will not be subjected to the strain of being tilted head downwards. Cisternal puncture is also indicated if a block has been demonstrated by a previous lumbar puncture or by Myodil introduced by the lumbar route. The slow absorption from the subarachnoid space is an advantage because Myodil introduced cisternally will often seep past an apparently complete block after twenty-four hours, and then screening with the head down identifies the lower margin of the block.

In addition, if an examination is inadequate or equivocal, the Myodil can be re-screened for many weeks after. The author is therefore in agreement with Davies (1951), who stated that he did not consider it necessary to remove the Myodil. The author would go farther and considers it positively undesirable to remove the Myodil because of the additional trauma which may occur to the subarachnoid space and the possibility of Myodil pulmonary embolism. After the Myodil has been introduced and the harness attached to the table, the patient is examined in the prone position. The lateral screening device makes the positioning of the Myodil infinitely easier especially in the difficult regions of the summit of the dorsal kyphosis and

in the upper cervical spine. It has become routine now to examine the clivus at the base of the skull and some surgeons occasionally ask for the Myodil to be placed over the diaphragm of the pituitary fossa in cases of pituitary tumours.

If the head is not allowed to rotate, almost all the Myodil can be drained back into the spinal theca with ease. Screening in the oblique and particularly in the supine positions is very important.

Two cases illustrate the value of screening in the supine position. In one of these (Fig. 5) there were multiple neurofibromas in the cauda equina, and a quite large one of these was only demonstrated by supine screening. The other case was of an extensive angioma lying on the posterior surface of the cord in the dorsolumbar region, and this was only convincingly shown by radiographs taken in the supine position.

If a block is found, to be sure that this is not due to spinal curvature, the patient should be tilted at least 70 degrees both in the prone and supine positions, and manipulated and gently shaken. Often this manoeuvre will reveal that an apparent block is at the summit of a spinal curvature. The new lateral screening device is of great value in demonstrating this.

Marking the level of the tumour.—If a block is found, its level should be marked by making a scratch on the skin at the level of the block. This statement needs qualification, because it is easy to place the marker inaccurately, thereby subjecting the patient to a more extensive operation than necessary and losing the confidence of the surgeon. There are three major causes for error. Firstly, the block may not be genuine. Using the technique previously described, it should almost always be possible to determine whether a block is genuine or not. The second cause for error is when radiographs are taken in one plane only, for example, the antero-posterior. If a lateral film is also taken, then the geometrical distortions inherent in a single antero-posterior film are cancelled. Thirdly, it is important to know the position into which the surgeon places the patient when he performs a laminectomy, as flexion of the spine may move a skin-marker as much as a whole vertebral segment.

The technique therefore is as follows: The patient is kept in a tilted position and a lead-marker is fixed to the skin of the back at the level of the myelographic block. Antero-posterior and lateral films are then taken; the relationships of the skin-marker, the myelographic block and the bony landmarks must be identical in both antero-posterior and lateral films (Fig. 6). Accurate positioning of the central ray of the

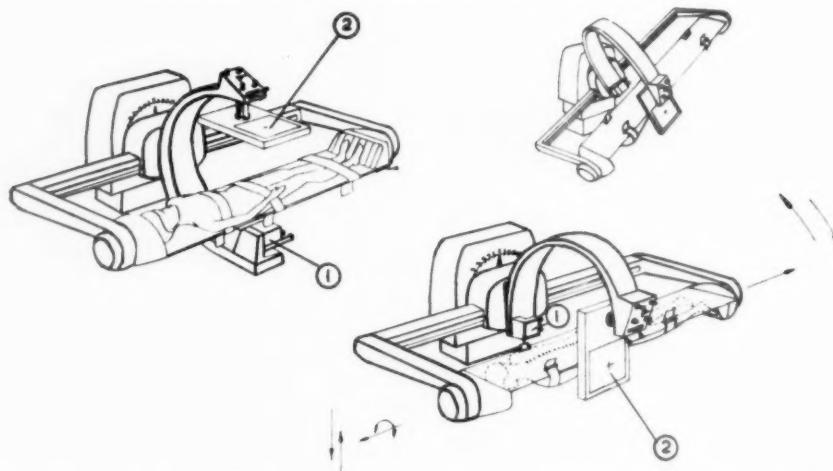


FIG. 7.—Diagram representing possible design of an X-ray apparatus to deal with the difficulties encountered not only in myelograms, but in barium examinations as well. (1) Represents the X-ray tube. (2) The screening and radiographic unit mounted on an arc so that they can rotate through 90 degrees. The patient is able to be tilted through 90 degrees head down and feet down and rotated at the same time, being enclosed in some sort of cocoon.

X-ray tube at the site of the block will achieve this. Then the patient is placed in the position adopted by the surgeon at laminectomy. Further antero-posterior and lateral films are taken. The Myodil, of course, will no longer be hard up against the block because the patient will be in the horizontal position. The amount of movement, if any, of the skin-marker over the spinous processes can be judged from the radiograph. The marker is then re-sited so that it lies at the level of the block in the position favoured by the particular surgeon at laminectomy. It is firmly fixed with the fingers and a scratch made on the skin alongside it. This makes for accurate localization.

The apparatus described is by no means ideal, and Fig. 7 indicates possible developments of an apparatus which will answer some of the problems in many X-ray procedures, in particular, myelography. The patient would be enclosed in a cocoon and could be rotated as well as tilted. At one end of an arc the screening and radiographic unit would be placed; at the other end of the arc the X-ray tube. This would rotate about the patient. Thus only one tube and fluoroscopic unit would be necessary to take films in any position throughout 90 degrees. The patient could also be rotated as he is tipped and the contrast medium might therefore be

made to cover all the limits of the spinal subarachnoid space.

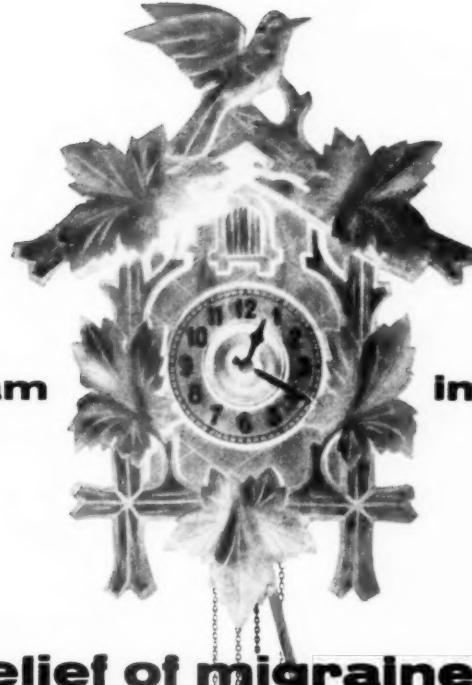
All the manœuvres mentioned have been described before but it was felt that the principles of efficient myelography should be re-stated, as with new equipment they can be more easily and rapidly performed. It is important to indicate how attempts to improve the accuracy of radiological diagnosis in this examination are being made, so that patients will suffer as few ill-effects as possible.

Acknowledgments.—The author is grateful to the physicians and surgeons of the West End Hospital for Neurology and Neurosurgery, and the Westminster Hospital, for allowing him to have access to their cases, in particular to Mr. Geoffrey Knight and Mr. Leslie Oliver. Also to Mr. E. J. Steadman, Senior Engineer at Messrs. Watsons.

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Dr. J. W. D. BULL showed a film entitled **Some Practical Principles in Contrast Neuro-radiography**.



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Section of Obstetrics and Gynaecology

President—H. J. MALKIN, F.R.C.O.G.

Meeting
February 26, 1960

DISCUSSION ON HYPNOSIS IN OBSTETRICS AND GYNAECOLOGY

Mr. V. B. Green-Armytage (London):

Hypnosis in Gynaecology

Hypnosis is a subject new to this Section but in reality is very old, for it is inferred a score of times in the Bible, particularly in the Gospels, the Acts of the Apostles and the Book of Timothy.

Just over one hundred and twenty years ago Dr. James Esdaile, a Scot practising in Calcutta, was the first to use hypnosis for surgical purposes. He not only carried out hundreds of operations under hypnotism but, far more important, trained a large number of assistants to carry on post-hypnotic suggestions whilst he performed the operation. Eighty years later I followed in his footsteps.

Gynaecology.—First, take the schoolgirl at puberty, or the girl far beyond puberty with dysmenorrhoea, menorrhagia or phobias going on sometimes to hysterical attacks: 90% of such cases are stress conditions, anxiety states or defence mechanisms, actuated by a desire to excite attention and sympathy or to escape unpleasant duties. Such girls or young women are excellent subjects for hypnosis and can readily be cured in one to three séances.

Amenorrhoea may follow attempted coitus, and is common following emotional upset. It was reported in the war, and particularly amongst prisoners in Belsen and Dachau. Indeed, St. Joan suffered this way for the whole fourteen months in prison before her martyrdom in 1431.

Emotional amenorrhoea is very amenable to hypnosis just as is psychosomatic pelvic pain, menorrhagia, or hyperemesis gravidarum due to a suppressed or hidden guilt complex.

Infertility.—By the same mechanism there is not the slightest doubt that the over-tense, anxious, spasmophilic, sterile wife can often be enabled to conceive through hypnosis; I have records of over a score.

In others, frigidity and dislike of the feminine role can often be made to disappear. An example of such frigidity is the apparently normal and happy couple who, despite every investigation, are childless. Then of a sudden the wife goes astray with the lodger and within a month is pregnant. So common are these cases that the French have coined a maxim

“la meilleure guérison d’infertilité est un locataire bien fort”.

Another aspect of infertility is the wife who states that her husband is “no good” and cannot stand up to normal function. Such a condition not only creates a profound inferiority complex in the husband, but often produces hatred and repugnance in the wife. It is very important to know that these distraught husbands can be helped by an understanding hypnotist.

Insomnia.—This may seem a minor condition but as an anxiety or fear state it is a thing of dread to the post-menopausal woman, and sometimes to the post-operative or post-natal patient.

This symptom should not be lightly dismissed with drugs, for it is readily cured by the laying on of hands. This technique is mentioned more than thirty times in the New Testament, and should be combined with the requisite suggestions, but since recurrence is not uncommon, I strongly advise the use of a simple method of post-hypnotic suggestion which consists in asking the patient, if she awakes or cannot sleep at night, to hold the hypnotist’s visiting card above her eyes and repeat the one word SLEEP which has been written thereon. In most cases this works wonderfully, but in some it is necessary to ventilate some past or hidden incident in her life which worries her and keeps her awake. To do this hypno-analysis is often successful, but this infers a deeper stage of hypnosis.

Vaginismus and dyspareunia are notoriously difficult to treat and too often end in disappointment and failure. In 90% of such patients it is not a matter of pain, tension, or even fear of pregnancy, but rather that there exists an Oedipus complex going back to childhood where the love of a father has been rejected or destroyed, resulting in reversion to a mother fixation. Sometimes a revenge complex exists wherein sadistic resistance to a husband becomes pleasurable for the very reason that he is the imago of her father.

As hypnotism, hypno-analysis, and even prolonged psycho-analysis often fail in these cases, I am inclined to combine simple second-stage hypnosis with the use of Prococaine injections at 3, 6 and 9 o’clock of the outlet, under anaesthesia.

The patient complaining of dyspareunia in whom bimanual examination is easy and uninhibited is, as a rule, a homosexual who uses the symptom as a defence mechanism against her husband, who may be also at heart one of these.

Finally, the case of advanced cancer, with or without metastases and accompanied by gross constant pain, can be greatly relieved by hypnosis.

Methods.—A confident and competent hypnotist will succeed in 90% of the cases he attempts whether in the quiet of the consulting room or the noise of an outpatient department.

The patient who boasts or proclaims that she cannot be hypnotized should be told that it is nothing to be proud of as it is only those of the lowest I.Q. who cannot be put to sleep, for the simple reason that they have not the ability or power to make their minds a blank and relax.

With a reliable witness at hand it should be clearly explained to the patient when she is seated or prone, and is comfortable and warm—a very important thing—that she will hear every word said and that her subconscious mind will register it, that she will do what she is asked, and that gradually she will float into a state of drowsy relaxation, where nothing matters or she will feel too lazy to bother.

To induce hypnosis at the first few séances I usually hold a sixpence, a light or a fountain pen before and above her eyes and ask her to concentrate upon that and nothing else. I then say, and repeat again and again, "your lids are heavy, you want to close your eyes, close your eyes—sleep—deeper—deeper"; at the same time with circular motion I gently compress the eye-balls with middle finger and thumb. I then say "breath in and out deeply, deeply", repeating every suggestion again and again. As she gets more and more drowsy, I tell her to take a deep breath and suggest that her limbs are growing heavy; that she cannot lift them; that she cannot open her eyes—sleep deeper and deeper.

In this light stage of hypnosis it is possible to suggest for instance that the pain or the bleeding will not recur; that it has now gone and will not return; that her fears, her anxieties no longer exist—they have passed and gone; "that she will wake in five minutes by the clock, happy and feeling well—not forgetting".

If she is *en rapport* with the hypnotist and a deeper stage is desired for medical reasons, or if she has already attained that stage because she is an excellent subject, he should take hold of one arm or leg and tell her that the muscles are getting rigid and stiff and that she cannot bend it. As this stage of tightening of muscles is reached, and it is necessary to break down adhesions or open a whitlow, then he should tell

her that she has lost all feeling below the wrist and that she can feel nothing—nothing.

Should he desire to get the patient still deeper he repeats the words "you are sound asleep; you have lost all control of your body; you feel as if your body had floated away; you cannot stand up; you cannot walk; and if you try you will fail. You are now an automaton and will answer any straight question that I ask; you will not awake although you may open your eyes".

At this stage he can ask the patient to make any automatic movement, such as rotating one hand round the other. The patient is now in the stage of somnambulism.

It is worth remembering that patients who do not speak English readily enough can be treated by transfer hypnotism. That is, a friend or interpreter stands beside the hypnotist who then asks the patient as before to gaze at a light or pencil. He repeats and repeats the usual sleep talk as before, whilst in the same breath and in the same monotone, his words are translated to the patient by the interpreter.

Mr. M. D. Arwyn Evans (Cardiff):

Initial Impressions of Hypnosis in Obstetrics

My contribution to this discussion will describe my experiences and impressions of hypnosis in obstetrics during the last nine months, never having practised hypnosis consciously before. I shall also try to answer the following queries: How difficult is it to hypnotize a person? Does hypnosis require a lot of practice? What percentage of the population can a beginner hypnotize? How useful is it in obstetrics and should all obstetricians be able to use it when necessary?

About twelve months ago a letter was received at the Antenatal Clinic in Cardiff which read: "Can I have my baby in the hospital under the State and under hypnosis?" After much discussion it was decided to see the patient and she was asked to report. The patient, the antenatal sister, my registrar, house surgeon and I congregated in a quiet room in the hospital and got to work. The result of the séance was that I completely failed to hypnotize the patient. She was so anxious to be hypnotized that she fell asleep as soon as I started to talk to her. This patient was admitted a week later, developed primary uterine inertia and the labour was terminated by a Cæsarean section. This may have been a coincidence, but it is possible that she had lost confidence in the staff who failed to hypnotize her. The first lesson to be learnt from this failure, I thought, was that the patient felt that the fault was mine and not hers. I wanted a method in which the failure would be inter-

preted by the patient as her fault and not mine. In this way I would keep the patient's confidence.

I see the patient in a warm room. This is most important, as it is very difficult to hypnotize a patient on the first occasion if she is cold. She sits in an arm-chair and gets quite comfortable and relaxed. She is then asked to place her hands on her thighs or knees and told to concentrate on the right hand. She is told that after a short while her hand and arm will begin to feel lighter and lighter like a balloon and as it feels lighter it will start to rise off the leg and she will begin to feel sleepy and tired, her eyelids will get heavier and heavier and she will feel that she will have to close them. It is most important when giving these suggestions that one keeps up a repetitive patter in a monotonous voice.

At least 90% of the patients will fall into a light sleep on the first visit. Pregnant women seem to be particularly susceptible. They are obviously anxious to relax and to have their babies easily. About 35% will remain in a light trance (Group A), 40% will progress into a medium trance (Group B), and about 15% into a deep trance (Group C). In my opinion one can be fairly sure into which group these patients belong after their first visit.

The patient is usually in a light trance in about two minutes. The usual methods of deepening the trance are then used, e.g. hand levitation and rehypnosis, &c. When one is satisfied that she is in as deep a trance as possible her suggestibility to anaesthesia can be tested. An area on the back of one hand is outlined and she is told that this part will become numb and cold and that she will not feel anything sharp when it touches her. Her reaction to a pin is then tested. One can also outline the back of the other hand and tell her that it is extremely sensitive and that she will feel anything that touches her on this part very acutely and sharply. Then this part is touched with the blunt end of a pin and her reaction noted. Her reaction to these tests decides the group to which she belongs. If one is unable to produce anaesthesia she is in Group A. Those in whom one does produce anaesthesia belong to Groups B and C. When the patient is in Group C she is a somnambulist and one can stick a needle through the skin without producing any pain at all. It is on those in Group C that surgical operations can be performed under hypnosis.

I see the patient antenatally on three or four occasions. If she is in Group A and in an ordinary Maternity Unit she will not be helped very much during her childbirth. She may sleep a little between her pains but she will definitely feel them and in my opinion should be treated as an ordinary patient with drugs if necessary.

One should not raise this patient's hopes with regard to a painless childbirth. Another important point is that if one has promised the patient to see her during the confinement and for some reason or other is unable to do so, she will become more scared and worried and may develop a primary inertia. Therefore if one is not prepared to be with the patient during the confinement one should not use this therapy. I am not referring, of course, to units specially trained in this treatment.

Groups B and C are very suitable for labour under hypnosis. Post-hypnotic suggestions can and should be used in these cases. Forceps can be applied and episiotomies performed without the patient feeling pain. If, however, the patient is a little tense some local anaesthesia can be used as well. If the patient is in Group C she can be made to go into a trance very easily and quickly and the hypnotic control can be transferred to someone else. In my opinion the patients who have had babies under hypnosis are much fitter and less liable to shock. They probably lose less blood and are certainly extremely grateful and will not be afraid of any future confinements. They can eat a large meal immediately after the labour and feel remarkably well.

The following incidents, which have occurred in my practice during the last nine months, emphasize these points. I was called to see one of my first patients who was experiencing quite a lot of pain at 3.00 a.m. when the os was three fingers dilated. She was in Group B, was easily hypnotized and while under hypnosis I told her that I was leaving her and that she would not have any more pains. At 9.00 a.m. the same morning I saw her again; she was quite fit and literally had had no more pains. I seemed to have stopped the labour completely. Obviously I had used the wrong words and should have said that the contractions would be painless or they would be present but would feel quite pleasant.

In another case when I was using the hand levitation method, I told the patient to look at her hand and in half a minute the hand started to rise and she went to sleep. When she awoke I asked her how she felt and she said "a strange thing happened, I was looking at my left hand but my right hand started to rise". I had forgotten to tell her which hand to look at. I was concentrating on the right hand.

A patient in Group B, who was having her second baby, was hypnotized at the onset of labour and told that she would not feel any pain at all until the head came on to the perineum. I am told that she lay quite still for four hours, only beginning to move when the head began to stretch the perineum. I rehypnotized her and she had a completely painless labour.

In my first case in which forceps were applied under hypnosis I woke the patient up as soon as the baby was delivered and showed it to the mother. Both patient and obstetrician were extremely pleased and delighted. I then told her that I was going to put her to sleep again as we had to put a few stitches into the perineum but I failed completely to hypnotize her. The patient had had what she wanted and was not interested any more in hypnosis. I think this is most significant.

My conclusions of this last year's work are these: Any doctor, with few exceptions, who is interested in hypnosis can use this therapy. Obviously some, as in surgery, will have better techniques than others and will take to it more easily. One must be careful in selecting the first case in order to give oneself confidence. Enthusiasm is of great help. 90% of pregnant women can be hypnotized but only 55-60% will have any real benefit from it during labour. In other words every other patient one sees can be helped greatly by this therapy. In my opinion one can find out at the first visit if this therapy will help a particular patient or not. Hypnosis should therefore be within the capabilities of every obstetrician.

Mr. S. D. Perchard (London):
Hypnosis in Obstetrics

Some indication of the incidence of suitable subjects is seen in a small series of primigravidæ (Table I) in whom group hypnosis was attempted.

TABLE I.—TRANCE INDUCTION. PRIMIGRAVIDÆ

Failure	17 (22%)	i.e. no response
Moderate	19 (25%)	Subjective and occasional slight objective response, e.g. limb heaviness
Good	31 (41%)	Objective response, e.g. limb immobility, pinprick anaesthesia or simple post-hypnotic suggestion
Somnambules	9 (12%)	Deep trance and wide range of phenomena obtained
Total	76	

The criteria used are an index of suggestibility and not of trance depth, because the latter is a complex entity which has so far defied measurement.

The direct use of hypnosis during labour is difficult to arrange on a large scale and a trial at Mile End Hospital was therefore planned to investigate the effect of post-hypnotic suggestion given during the antenatal period. It was restricted to primigravidæ.

A simple standardized technique was devised, which was used by midwives with no previous experience of hypnosis and which enabled them to deal with groups of up to 16 patients.

A trance induction having been attempted, all the patients, irrespective of their response, were

told that they would be relaxed and sleepy during labour and consequently unable to feel or remember any pain. Strengthening contractions and the sensations of the second stage would be interpreted as encouraging signs of progress and would not therefore be painful or unpleasant. They were told they would remember very little about the labour except the actual delivery and would be unable to feel or remember any interference by the doctor or midwife, should this become necessary.

For control purposes three different programmes were arranged, in each of which the mother must volunteer to attend three classes during the last eight weeks of pregnancy, viz.:

Programme A: Three simple instructional talks, including a visit to the labour wards.

Programme B: As in A, with the addition of three relaxation classes conducted by a physiotherapist.

Programme C: As in A, with the addition of three sessions of hypnosis as already described.

Except for mentally unstable patients, unmarried mothers and patients from outlying areas, all primigravidæ who booked for confinement and who accepted the invitation to attend classes were enrolled in serial rotation into one of the three programmes. The patients were kept unaware of the differing methods of preparation.

The study was commenced in October 1953 and Groups A and B were continued for two years. Group C has been continued up to the present time and the results up to the end of 1959 are included.

Management during labour was the same for all three groups, the labour ward staff being usually unaware to which group the patient belonged. They were encouraged to help all patients to relax and sleep during the first stage and between contractions in the second stage.

Objective information concerning behaviour during labour was recorded at the time, by the staff. One week later, the mothers were questioned about their subjective experiences during the labour and six weeks after delivery they were asked whether the preparation had helped them a great deal, slightly or not at all.

Additional information from all the primigravidæ who were delivered in the hospital during the six years of the trial, but who did not volunteer for the classes, is shown under Group D.

The four groups are summarized in Table II.

Group preparation	No. of patients
A. Lectures only	268
B. Lectures and relaxation class	126
C. Lectures and hypnosis	986
D. Nil (non-volunteers)	1,703

TABLE III.—GROUP C: ABILITY AS HYPNOTIC SUBJECTS

Good	547 (55.5%)
Moderate	257 (26%)
Poor (failures)	182 (18.5%)
Total	986

Table III shows the results of attempted hypnosis in Group C patients. The criteria were those mentioned above except that the incidence of somnambules is not known, as no attempt was made to deepen the trance to this stage. The figures resemble those of the first series and sample checks from time to time throughout the trial have shown a remarkable consistency in this incidence of susceptibility to hypnosis.

The allocation of patients to the groups would have been better done by random selection, but the characteristics of all three groups, as shown by age distribution, mode of delivery, &c., were all very similar, indicating that selection was unbiased. The only difference in modes of delivery was a slightly higher forceps rate in Group D which might be in part attributable to better co-operation among the volunteer patients.

Most of the other objective findings, e.g. abnormalities and durations of labour, showed no difference between the groups. There was, however, a slight difference in the amounts of sedative and analgesic drugs needed (Table IV).

Group C contained significantly more patients of the "less than 100 mg pethidine" category ($P < 0.05$) and this difference was due to the mothers who were susceptible to hypnosis ($P < 0.01$).

TABLE IV.—SEDATION DURING LABOUR (PERCENTAGES)

Group	Pethidine			
	Less	100 mg	200 mg	More
A	32	40	15	13
B	34	39	14	13
C	40	38	11	11
Good	44	36	11	9
Moderate	43	38	9	10
Poor	26	43	13	18
D	35	32	15	18

Less than 100 mg pethidine includes no sedation, or potassium bromide, chloral or Doriden.

More than 200 mg pethidine includes morphine preparations, scopolamine, paraldehyde, barbiturates, other than phenobarbitone, with or without pethidine.

The incidence of general anaesthesia for forceps delivery in Group C patients (10%) was half that of the other groups. Since the commonest indication for general rather than local anaesthesia was lack of co-operation, the difference could be a result of the preparation.

Observations on the patients' behaviour during labour showed no significant difference in calmness, relaxation, co-operation, &c., although the

Group C patients were, on the whole, slightly better. Co-operation was, for instance, good in over 80% of Groups A and B and in 94% of Group C.

Whilst not more than 20% of patients in any group were judged by their attendants to have had severe pain at any time during labour, 32% of Group C and over 50% of Group A and B patients themselves recollected severe pain (Table V). Of these, about 1 patient in 6

TABLE V.—SUBSEQUENT RECOLLECTION BY PATIENT (PERCENTAGES)

Groups	A		B			C		
			Total	Good	Moderate	Poor		
Pain:								
Nil	4	5	5	5	7	2		
Not severe at any time	44	42	63	69	65	44		
Severe	52	53	32	26	28	54		
Amnesia:								
Marked	15	15	20	24	18	12		
Partial	44	41	49	48	48	50		
Nil	41	44	31	28	34	38		

remembered severe pain during a large part of the labour; the remainder did so for a short time only, usually during late first stage or with the crowning of the head.

The incidence of amnesia was not significantly greater among the Group C patients; furthermore on later questioning, mothers who originally had marked amnesia were often able to recall a good deal of the labour. This supports the view that hypnotically induced amnesia is of a superficial nature. Since the inability to recollect pain appeared to be unrelated to amnesia for other events, some direct analgesic effect of the suggestion seems possible.

38% of Group C mothers found labour a pleasant experience compared with 18% and 24% of Groups A and B. The difference is significant ($P < 0.01$) and is due to the hypnotically susceptible mothers in whom 42% of labours were pleasant.

More patients (78%) thought they had been greatly helped by their preparation in Group C, but the difference, though statistically significant, could not be said to be important. In Group B help was usually attributed to the breathing exercises.

There was no difference in the proportions of mothers (70%) who were anxious to have more children.

It would appear that no detectable benefits were derived from the simple relaxation exercises and that not more than a limited subjective benefit with slightly reduced need for sedation resulted from the hypnosis.

This scarcely does justice, however, to the confidence and satisfaction which many mothers derived from the latter preparation. Remembering the limited and stereotyped preparation, it is

submitted that, in return for a modest expenditure of time and effort, the results do not compare unfavourably with those of the continental method of psychoprophylaxis, which involves elaborate antenatal preparation and close individual support during labour. Moreover, the published reports of their personal experiences by mothers who have been prepared by the latter method suggest that many of the so-called painless childbirths would have been classified as cases of moderate or even severe pain in our series.

It seems that much of the success of psychoprophylaxis, as with Dick-Read's method, depends upon the enthusiasm and support which is given to the mother during labour, by an attendant whom she knows and who has helped with her preparation. There is little doubt that our results with hypnosis would have been greatly improved had a comparable arrangement been possible. Further improvement would also have resulted by widening the scope of the suggestions given, in particular by trying to develop a stronger maternal attitude among the less mature patients.

From experience of patients whom I have personally prepared and delivered, I can certainly testify to the remarkable degree of control and co-operation which is possible with hypnosis in good or even moderate subjects, many of whom can be kept asleep for the greater part of the labour, with little or no sedation. Operative procedures may often be performed without disturbing them.

This method of individual management is, however, too limited by practical considerations to have a wide application; moreover forceps deliveries, &c., may sometimes be performed without anaesthesia, though usually much less easily, in co-operative unhypnotized patients.

It cannot be over-emphasized that the methods of inducing hypnosis are merely techniques which may be acquired by anyone. *They need not and for obstetric purposes should not involve any form of domination of the subject.*

Despite many reports of the successful use of hypnosis in obstetrics it has never been taken up on any scale. One of the undoubted reasons for this is the resentment aroused in the minds of many people at the idea of mental domination of one person by another. For this reason alone, domination techniques should be avoided despite the more dramatic initial successes which are sometimes obtained. Another objection is the overdependent attitude which sometimes results in the patient. There need therefore be no variation in the normal relationship between

the patient and an obstetrician in whom she has confidence.

The technique devised for the midwives' use was based on the conventional principles of trance induction which are as follows:

(1) The subject's attention must be held by one means or another, to the increasing exclusion of outside stimuli. For this patients were asked to close their eyes and concentrate on deep breathing with progressive relaxation.

(2) There should be an accompanying soothing, monotonous or repetitive stimulus which may be visual, auditory or tactile. In this case it was supplied by the timing and intonation of the midwife's voice.

(3) Attempts should be made to obtain responses to increasingly complex suggestions, thereby increasing suggestibility. In our case this was done by obtaining responses where possible, in the following order: (a) Arm heaviness or levitation. (b) Feeling of warmth or cold. (c) Inability to bend an arm (catalepsy). (d) Anaesthesia of the hand to pin-prick.

When response to the above was satisfactory, the patients were then taught self-induction of the trance and of anaesthesia, by means of post-hypnotic suggestion.

To those who consider that any form of psychological preparation for childbirth is valueless, hypnosis will at best be of interest as a bizarre phenomenon with limited application in obstetrics.

Those who believe that some mothers have a genuine need of some such preparation will have considered the relative merits of the Dick-Read method, psychoprophylaxis and hypnosis. The part played by relaxation exercises and controlled breathing in these methods is uncertain. Hypnosis is sometimes said to be a form of Pavlovian conditioning, on the other hand even many of their supporters admit that suggestion plays a large part in the other methods.

Since suggestibility is known to be greatly increased by hypnosis and we have seen that between 50% and 80% of expectant mothers are hypnotically susceptible to some extent, it would seem a logical step to devise an antenatal programme which combines some form of hypnotic technique with the best elements of the other methods.

In conclusion, I should like to thank the maternity staff at Mile End Hospital for their co-operation, in particular Miss Blackstock and Miss Davies, the two midwives who have done most of the hypnosis. Acknowledgment is also due to Dr. Stewart Morrison of the London Hospital for his statistical advice.

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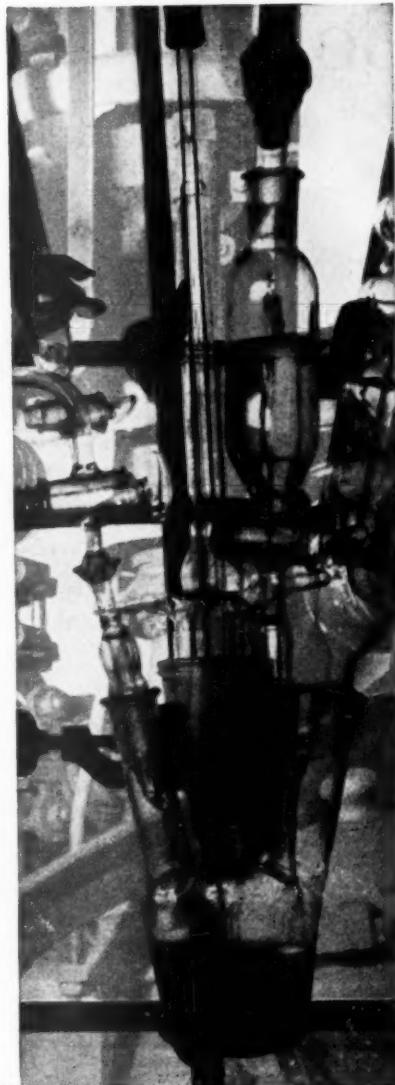
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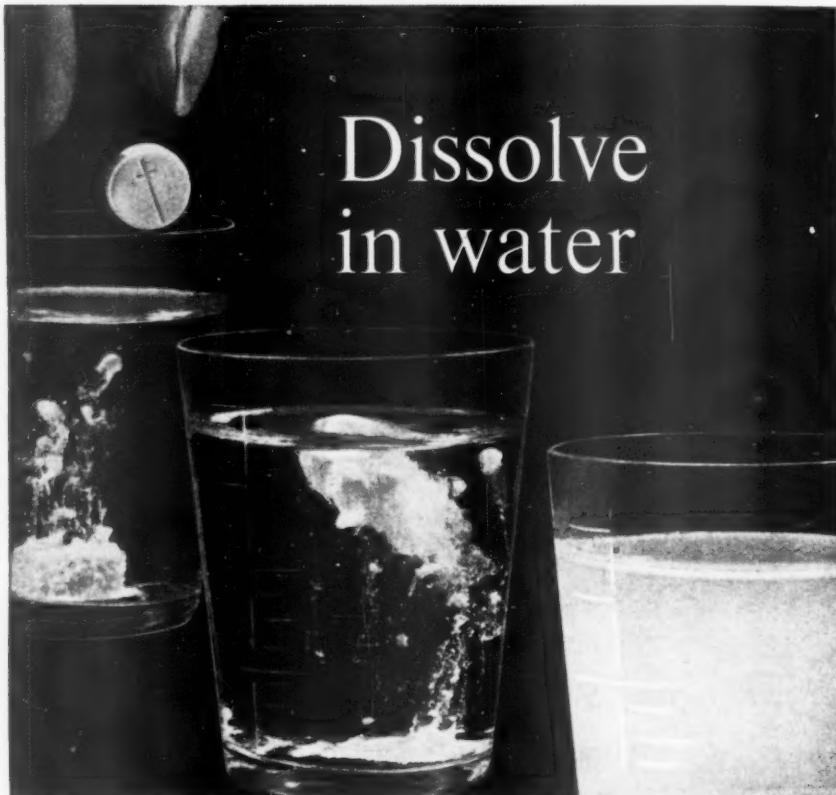
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Meeting
December 4, 1959

PAPERS were read as follows:

A One-stage Pharyngo-oesophago-laryngectomy in which the Anterior Portions of Larynx and Trachea were used for Reconstruction.—Mr. J. F. SIMPSON.

Discussed by Dr. I. SIMSON HALL, Mr. R. D. OWEN, Mr. H. J. SHAW, Mr. K. G. MALCOMSON.

Closed Injuries of the Larynx and Pharynx.—Mr. D. L. CHADWICK.

Discussed by Mr. A. BOWEN-DAVIES, Mr. J. ANGELL JAMES, Mr. S. W. ALLINSON.

Cystadenoma of the Larynx.—Mr. E. F. STEWART.

Discussed by Mr. W. A. MILL, Mr. MAXWELL ELLIS, Mr. F. G. COLLINS, Dr. R. L. FLETT.

Laryngeal Spill-over Treated by Intra-laryngeal Operation.—Mr. H. S. SHARP.

Mr. Sharp's paper has been published in the *Lancet* (1959, ii, 492); the other three papers will appear in the *Journal of Laryngology*.

Meeting
February 5, 1960

PAPERS ON **Tracheostomy and Controlled Respiration** were read by Mr. IVOR FREW and Dr. E. A. COOPER.

The subsequent discussion was opened by Dr. E. A. BLAKE PRITCHARD, Mr. WALPOLE LEWIN and Dr. R. A. BEAVER. Mr. T. M. BOYLE, Mr.

J. W. T. DIXON, Mr. ROBERT EVANS, Dr. H. B. C. SANDIFORD, Mr. H. V. FORSTER and Dr. W. H. KELLEHER also took part in the discussion.

The meeting will be published in the *Journal of Laryngology*.

Meeting
March 4, 1960

DISCUSSION ON THE SALIVARY GLANDS—PHYSIOLOGY, PATHOLOGY AND TREATMENT

Dr. Herman Diamant (Stockholm, Sweden):

Recent Research on Physiology of the Salivary Glands

The study of the large salivary glands lies on the fringes of different specialties and for this reason it has not been altogether satisfactory. It is only during the last few years, at all events in Sweden, that diseases of these glands have been the concern exclusively of the otologists. Physiologists had very early observed that the salivary glands were ideal for investigation. They were the only digestive glands whose secretion was readily accessible and whose responses to various stimuli could be studied without the use of unduly intricate apparatus. Not only were they studied from the purely physiological standpoint; they were also used as tests of conditioned reflexes and here it was the Pavlov school, and notably Krasnogorsky, who pursued traditional Russian research.

In recent years numerous teams in different parts of the world have been investigating the

physiology of the salivary glands, with special reference to their secretion and its normal variations. Names that come to mind are Denton in Australia, Schneyer in the U.S.A., and Emmelin in Sweden.

I have been able to follow the work of Emmelin and his associates at close quarters. Emmelin and his principal co-worker, Strömbäck, have among other things been interested in two aspects: first, paralytic-secretion following denervation, and secondly, the activity of the salivary glands evaluated on the basis of their oxygen consumption. Emmelin and Strömbäck have shown, notably, that denervation of a salivary gland by section of the chorda tympani leads, after some time, to an increased secretion from the ipsilateral submandibular gland on stimulation with, for example, adrenaline. The effect of atropine, together with preganglionic and postganglionic nerve section has been tried; several of the experiments, of course, can easily be performed on human subjects, and it was

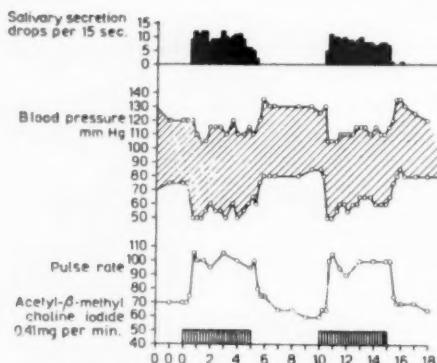


FIG. 1.—Normal infusion experiment.

intended to see if the results were valid in man. By a coincidence one field of application for this theoretical research immediately arose, since quantitative investigation of the secretion was an excellent means of checking antidotes to cholinesterase-inhibiting organic phosphorus compounds such as "nerve gases".

Concentration of the clinical and theoretical treatment of all diseases of the salivary glands in the Ear, Nose and Throat Department seemed a very sound policy, for the department had taken over in 1949 all cases of tumours of the salivary glands. These cases at present number about one hundred annually. At the same time other cases with disorders of the salivary glands were included, especially patients with chronic parotid enlargement.

The best method for determining the volume of secretion was found to lie in slow intravenous infusion of methacholine, acetyl-beta-methyl-choline iodide, which induced very profuse secretion (Fig. 1). This could be arrested by administering atropine, which proved to be the best counter-agent (Fig. 2). It was found that atropine appeared to be absorbed more rapidly after subcutaneous than after intramuscular injection, which was in itself remarkable.

The atropine tests were followed by a series of experiments designed to elucidate the effects of

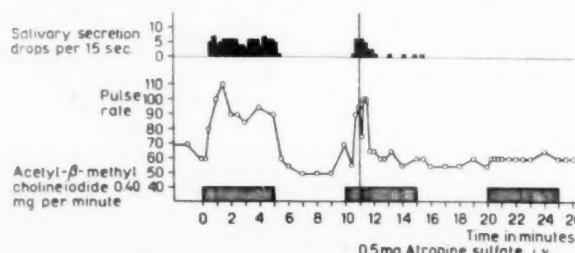


FIG. 2.—Effect of atropine on stimulated salivary secretion.

various drugs on the activity of the salivary glands. It was found that atropine in a dose producing no side-effects was the most efficacious of the anticholinergics for pre-operative blocking of the secretion. Other agents which had the same effect as atropine often produced serious side actions, chiefly on the heart.

No normal values for saliva secretion had thus far been reported, and it was desirable to get some idea of the normal range. First, however, we wanted to study the resting secretion as Schneyer, among others, had described it. As regards the parotid secretion, an amount of less than 50 mg per five minutes was considered permissible before we could speak of resting secretion. This meant that at least one drop had to fall during that length of time.

In the absence of stimulation there is usually no secretion whatsoever from the parotid gland, as has been shown by tests lasting for one and a half to two hours. On the other hand, there are persons who normally have some resting secretion (Fig. 3). We do not yet know if these are

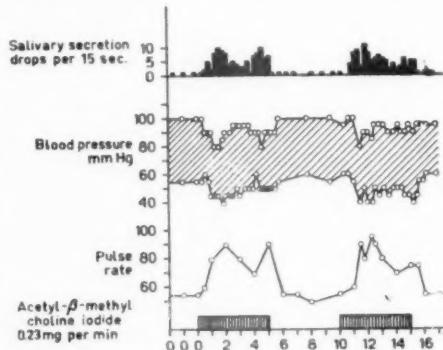


FIG. 3.—Normal infusion experiment showing resting secretion between two five-minute periods of stimulation.

especially sensitive individuals in whom even the very slight excitation caused by the sialometer evokes the secretion, or if the secretion is a genuine one.

Corresponding tests on the submandibular gland—where the use of a sialometer is generally impracticable and a fine plastic catheter has to be introduced for collection of the saliva—inevitably show a resting secretion. This secretion, unlike that from the parotid gland, is not arrested by injection of atropine, even in large doses. Probably it is elicited via the sympathetic.

We have also attempted to collect the secretion from the sublingual and submandibular glands by using an appliance of sialometer character; that is to say, without insertion of a catheter (Fig. 4). The resting secretion is then somewhat less, which suggests that the catheter itself has some stimulating effect. The decrease is equivalent to that produced by atropine.

In other experiments the chorda tympani has been stimulated in human subjects. These experiments were performed on patients who underwent tympanotomy for otosclerosis or for diagnostic purposes, and in whom section of the chorda tympani was considered feasible. We know from experience that division of this nerve does not, as a rule, cause any discomfort. Occasional patients complain of an impairment or change of gustation in the anterior two-thirds of the tongue. On questioning, patients in rare instances report that they have noticed some change in the sense of taste but that it has not distressed them.

In cases where the chorda tympani has definitely been left intact, we have later found that its function may be impaired. The impairment consists in loss of gustation in the anterior two-thirds of the tongue and failure of lemon to elicit a saliva secretion. It has been observed to persist as long as one year after the operation.

Stimulation of the chorda tympani during operation produces very characteristic responses.

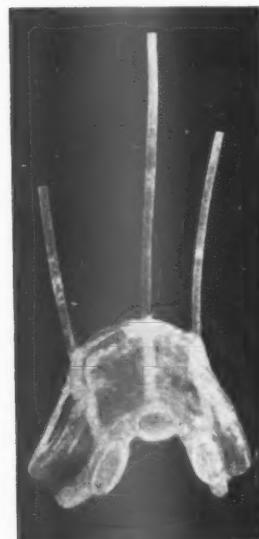


FIG. 4.—Individual prosthesis for collecting saliva from the sublingual glands.

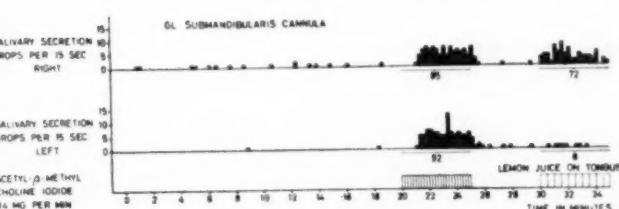


FIG. 6.—Comparison of salivary response of submandibular gland to an injection of acetyl-beta-methylcholine and to the application of lemon juice on the tongue. Bilateral recording with the chorda tympani cut on the left side.

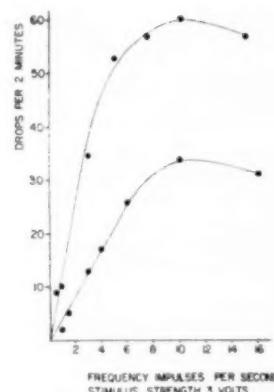


FIG. 5.—Effect of increased impulse frequency on secretory response in two different persons to the stimulation of the chorda tympani.

Stimuli of 3 volts at a frequency of 10 per second elicit a maximal response of the same character as that observed on stimulation of other peripheral nerves (Fig. 5). The effect of stimulation of the chorda tympani ceases following injection of atropine.

At follow-up examination of the saliva secretion after section of the chorda tympani, a typical response is found. Methacholine evokes a bilaterally equal secretion, since in all probability it acts directly upon the secreting cells. Lemon juice poured on the tongue evokes a very sparse secretion on the sectioned side, due to severance of the afferent gustatory fibres and of the efferent secretory fibres (Fig. 6).

Studies reported so far have been concerned with the parasympathetic innervation. For the sake of completeness the significance of the sympathetic innervation also has to be elucidated. This is far more difficult in man, though a possibility does arise at major operations on the head and neck. Most of these are for carcinoma, but Swedish patients in this category have generally undergone intensive radiotherapy and

many of them are in fairly poor condition. We cannot, therefore, expose them to the hazards of a prolonged operation and without anticholinergic premedication, which is essential for stimulation experiments.

These investigations, which are one aspect of teamwork including electrophoretic studies of the saliva under various conditions as well as puncture experiments, have yielded initial results of some significance. We are still correlating the results with clinical findings in pathological conditions.

We have, however, gained a very good idea of the secretion under different conditions. The saliva secretion in man shows very great variability from one person to another, but in the individual subject there are only slight variations between the two sides and between the findings at repeated tests. It follows that an observed discrepancy between the two sides will generally point to unilateral disorder. This is virtually always a reduction of the secretion; genuine sialorrhœa occurs only as one of many symptoms in certain disturbances of the central nervous system.

I am not yet able to present exact figures for the saliva secretion after various types of stimulation. However, the order of magnitude of the stimulated secretion from the parotid gland can be gathered from the fact that infusion of 0.4 mg methacholine per minute for five minutes elicits 5.5 g, and 0.2 mg elicits 3.4 g. Stimulation with three drops of pure citric acid every 30 seconds on the extended tongue elicits 3 g over a five-minute period.

When the approximate range of the normally stimulated secretion had been ascertained, it was utilized, in the investigation of pathological salivary glands. Here we were mainly interested in patients with chronic enlargement of the parotid gland. Some of them had pronounced, others no appreciable xerostomia. This dryness is very conspicuous in many patients with disturbances of the salivary glands. Remarkably enough, even cases of very short standing present severe xerostomia, and in these there is no demonstrable secretion from the large salivary glands. This applies in particular to conditions associated with rheumatic diseases. It would seem that total xerostomia occurs only in cases of Sjögren's syndrome and in the long-standing, recurrent chronic parotitis cases without signs of systemic disease. It is clear that a more quantitative study of the secretion will not necessarily lead to the diagnosis. Supplementary electrophoretic and chemical examinations are invaluable aids, and if sialography and puncture

are added, the diagnosis should be established in most cases.

The need remains, however, fully to resolve the physiological problems concerning the normal secretion of the salivary glands, and in this brief outline I have simply touched upon various approaches. I would emphasize the necessity of pursuing the human experiments with due regard to results already achieved in animal experiments; for here, as always in physiology, we have to contend with the difficulty of anthropomorphizing our results.

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Sir Roy Cameron (London):

Pathology of the Salivary Glands

During the ten years 1948-1957, 176 salivary glands removed at operation were studied in the Pathological Department of University College Hospital. All of these were reported upon by me in the first instance and recently we have re-examined them in the light of further experience and with due consideration of present-day terminology. 74 of these specimens were inflammatory, and for the most part obstructive in origin, 102 were tumours. Table I summarizes

TABLE I.—DISTRIBUTION OF LESIONS IN SALIVARY GLAND MATERIAL REMOVED AT OPERATION AT UNIVERSITY COLLEGE HOSPITAL, 1948-57

Lesion	Parotid	Sub-mandibular	Sub-lingual	Total
Inflammatory and obstructive	22	51	1	74
Tumours	100	2	0	102
Total	122	53	1	176

the distribution of lesions in the three main sets of salivary glands; parotid lesions were more than twice as common as submandibular, despite the frequency of inflammatory and obstructive changes in the submandibular glands. The overwhelming preponderance of parotid tumours accounts for the discrepancy.

Inflammatory and obstructive cases, exclusive of nine instances of cysts and neoplastic obstruction of the main ducts, fall naturally into two main groups: those in which a salivary calculus was clearly responsible for the clinical, and presumably pathological, features and those where no cause was discovered but stone could be excluded (Table II). Table III compares the

TABLE II.—SALIVARY GLANDS SHOWING OBSTRUCTIVE LESIONS (U.C.H. 1948-57)

Gland	Calculus	Cyst	Cancer of floor of mouth	No cause found	Total
Parotid	12	2	—	8	22
Submandibular	32	3	4	12	51
Sublingual	1	—	—	1	1
Total	45	5	4	20	74

TABLE III.—MICROSCOPY OF SALIVARY GLANDS WITH OBSTRUCTIVE LESIONS (PERCENTAGES IN BRACKETS)

Microscopic changes	Calculus present	No cause for lesions
Distended ducts	41 (91)	12 (60)
Inflamed ducts	38 (84)	7 (35)
Periductal fibrosis	40 (89)	10 (50)
Myo-epithelial islands	6 (13)	2 (10)
Interstitial fibrosis	40 (89)	11 (55)
Diffuse lymphoid infiltration	35 (78)	13 (65)
Lymphoid follicles	32 (71)	13 (65)
Acinar atrophy	43 (96)	16 (80)
Total cases	45	20

main microscopic disturbances in the two groups. Clearly there is close correspondence in the frequency of acinar atrophy, lymphocytic and plasma cell infiltration of the interstitial tissue, including the formation of large lymphoid follicles, and myo-epithelial islands. Inflammation of the salivary ducts, periductal fibrosis and interstitial fibrosis with hyaline degeneration are common in both groups, but they are much more frequently the outcome of gross duct obstruction by calculus than of hidden causes. Some attention has been given to the latter twenty cases in an effort to discover their origins but without success. None suffered from mumps or any other form of inflammation; certainly there was no suspicion of calculous disease. Sex and age distribution agreed well in both groups.

From this study we conclude that prolonged disease of the salivary glands manifests itself by progressive atrophy of the acinar tissue, distension and inflammation of the large and small ducts, along with periductal fibrosis and more or less severe and extensive interstitial fibrosis. Lymphocytic and plasma cell infiltration are frequent, and often associated with the formation of large lymphoid follicles, some of which present germinal centres. The picture is that of steady parenchymal destruction, fibrosis, lymphocytic infiltration and lymphoid hyperplasia. To these may be added such inconstant features as polymorphonuclear and eosinophilic infiltration alongside smaller ducts, concentric masses of hyaline degeneration around larger ducts and new formation of small ducts. Proliferation of the myo-epithelial cells that line the medium-sized and larger ducts occurred in 8 of the 65 cases but it was seldom pronounced. In view of the importance attached to these myo-epithelial islands in the diagnosis of the Mikulicz and Sjögren syndromes I must emphasize their

occurrence in six instances of calculous obstruction of the main ducts. 2 of these cases merit attention since, microscopically, they closely resembled the Mikulicz-Sjögren picture.

Case I.—Mrs. F. G., aged 55, complained of a swelling of the left jaw for nearly eight months. The lump had been painless until two weeks before admission when she experienced severe pain and further swelling in the lump. Pus was seen emerging from the submandibular duct and X-ray examination disclosed a duct stone which was subsequently removed from a duct abscess, along with the submandibular gland. Microscopy showed severe interstitial fibrosis, acinar atrophy, distension, acute and chronic inflammation of the largest ducts, great lymphocytic infiltration with many large lymphoid follicles, along with myo-epithelial islands, collections of eosinophils and many goblet cells in the mucosa of the largest ducts.

Case II.—Mr. M. F., aged 39, gave a two years' history of a lump under the jaw that varied in size and was painful when large. The right submandibular gland was found to be greatly enlarged with pus flowing from its duct and a large firm calculus could be palpated in the duct. The stone and gland were excised. Microscopically, the gland closely resembled that in the previous case though myo-epithelial cell proliferation was not so pronounced.

The rest of our material—five examples of duct cysts and mucocoeles with associated parenchymal atrophy of varying degree, four instances of carcinoma of the mouth with submandibular duct invasion, obstruction and infection, and two specimens of sublingual atrophy and fibrosis—fits very well into the pathological picture already outlined. Myo-epithelial proliferation was not present in any of these cases but lymphocytic infiltration was often pronounced and fibrosis was extensive.

Our experience with 102 salivary gland

TABLE IV.—TUMOURS OF SALIVARY GLANDS (U.C.H. 1948-57)

Tumour	Site	No.	Percentage of group
Mixed salivary tumour (innocent)	Parotid	74	73
Malignant mixed salivary tumour	Parotid	4	3.9
Muco-epidermoid	Parotid	3	2.9
Squamous cell carcinoma	Parotid	2	1.9
Adenocarcinoma	Parotid	6	5.8
Acinar cell adenocarcinoma	Submaxillary	1	0.9
Adenolymphoma	Parotid	2	1.9
Oxyphil cell adenoma (oncocytoma)	Parotid	9	8.8
	Submaxillary	1	0.9
Total		102	100

tumours is summarized in Table IV. These were recently reclassified in accordance with the criteria adopted by Foote and Frazell (1954), without unduly upsetting our own conventions. The numbers are small and perhaps of limited value, but they depict a state of affairs similar to that recorded by observers in many parts of the world (Rauch, 1959).

All such hospital data give no true indication of the status of the salivary glands in disease although they may well serve to set the picture. We know that viral infections, in the form of mumps and the almost symptomless cytomegalic inclusion body disturbance, though common enough in children, may disappear without leaving behind any serious effects. So, too, we often meet with transient infections of the glands as a complication to surgery or oral sepsis, but very few pathologists have been afforded the opportunity of studying such material under ideal conditions. Nevertheless, a certain amount of information has accumulated as it were by accident or through errors of diagnosis and, along with valuable results derived from experiments on animals, affords the basis for a more formal sketch of salivary gland pathology.

Acute inflammation of the salivary glands may follow ascending infection of the ducts by many of the non-specific bacteria that frequent the mouth, or descending by specific and non-specific bacteria that reach the glands through the blood stream. In the first instance, the lesions produce periductal inflammation, in the latter the changes are predominantly interstitial. The parotid is most frequently involved. Apparently a normal salivary gland cannot be infected and either mechanical obstruction or pre-existing injury of the ducts or acini is necessary if infection is to take. In our experience post-operative parotitis is largely the outcome of infection with haemolytic streptococci or staphylococci, although pneumococci or *B. coli* may sometimes be concerned. Loss of acinar granules and even focal necrosis attributed to "stress" or "alarm" have been suggested as precipitating factors, but these are vague and hard to nail down. Sometimes this form of inflammation becomes chronic and recurrent in which case allergy, hormonal disturbances, nervous factors and deficiency states have been invoked as explanations. Women are more often affected than men and the condition passes into the ill-defined group of salivary swellings. The recurrent parotitis of children is often caused by *Streptococcus viridans* or pneumococci, and occurs as abscesses, diffuse suppuration or in an indolent form. There is no evidence of duct obstruction by calculus, no other systemic disease.

Viral infections include the common childhood complaint of mumps and the cytomegalic disease of very young children. Few of us get the chance to study the pathology of mumps but enough material has been collected, largely through mischance, to show that the outstanding features in the affected gland are capillary stasis,

interstitial oedema, localized infiltration of the connective tissue with lymphocytes, plasma cells and occasional clumps of polymorphonuclear leukocytes. Desquamation of the lining cells and consequent distension of ducts have been recorded. The neighbouring acinar cells may be compressed or even degenerate, and show inclusion bodies. Similar changes characterize the well-known complications of orchitis, oophoritis, pancreatitis and the rare meningoencephalitis, as well as the experimental lesions that may be produced by inoculating apes with the virus. Recovery is usually complete; what we want to know is whether mumps can smoulder on indefinitely with serious effects.

In cytomegalic disease of the newborn and sucklings epithelial cells of various organs—salivary, renal tubules, alveolar epithelium—enlarge, usually without inflammation, and display nuclear and basophilic cytoplasmic inclusions.

Chronic inflammation of the salivary glands still presents so many problems of aetiology, and indeed of pathogenesis, that we must, for the time being, be content to record observations. Chronic "sialectatic" parotitis with intermittent swelling of one or both parotid glands has been admirably described by Patey and Thackray (1955) who emphasize a progressive accumulation of lymphoid tissue around intralobular ducts, associated with epithelial hyperplasia and metaplasia. Secretory glandular elements atrophy and are replaced by masses of lymphocytes. There is no demonstrable blockage of the lumen of the ducts in the earliest stages and the cause has not been found. Fragmentation of the connective tissues supporting the intralobular ducts has been stressed by Patey and Thackray with the interesting suggestion that this allows the normal secretion of the gland to leak through the weakened wall with recurrent irritation and irreversible inflammation and fibrosis. There may be here a useful analogy with the leakage of bile from bile ducts when there is obstruction and fibrosis.

Prolonged calculous obstruction of the large ducts gives a broad spectrum of changes that has been referred to above. These changes are indistinguishable from the picture of chronic "sialectatic" parotitis; indeed, the description of Patey and Thackray would do perfectly well for a group of chronic inflammations involving any of the salivary glands and with a variety of causes. Since careful experimental investigation in animals, and information derived from the deliberate ligation of parotid or submandibular ducts in man, shows that duct obstruction makes these ducts distend, induces acinar atrophy and

stimulates fibrosis, and that cellular infiltration is not prominent, we are left with the problem of the astonishing lymphocytic infiltration and the lymphoid follicle production that is frequently a well-marked feature in chronic disease of the salivary glands. Our own experience makes us wonder whether this non-specific reaction may not precede calculus formation, leaving the latter to accentuate, and complicate, a slowly-smouldering reaction.

From the intriguing group of conditions long labelled Mikulicz's disease is being sorted out, at present, a sub-group which might well take over the original classification, Sjögren's syndrome. The unique features described by Johann Mikulicz (1892) were bilateral, chronic, painless hypertrophy of the lacrimal and salivary glands, in which most of the swelling was the outcome of a compact infiltration with lymphocytes, pushing aside and embracing the unchanged acini. Mikulicz regarded this as a chronic response to a low-grade infection and separated it from similar bilateral enlargements proved to be due to malignant lymphoma, tuberculosis and even acute inflammation. Modern investigations have shown that atrophy of acinar tissue may be severe and that ducts undergo a typical intra-ductal cellular hyperplasia which is largely the outcome of myo-epithelial cell proliferation. Some workers regard this latter proliferation as the most dependable method for distinguishing Mikulicz's disease from lymphoma. We have already pointed out that myo-epithelial islands are not uncommon in association with calculous obstruction as well as in the chronic non-obstructive inflammation. Indeed, we have formed the impression that the underlying pathological disturbance with these conditions is remarkably like that encountered in Mikulicz cases, so that the main reason for making the distinction is the unusual anatomical grouping of the lesions.

And now, by another strange twist of fortune, the Mikulicz story is being dealt a further blow. From pioneering observations of Gougerot (1925) in France and Sjögren (1933) in Sweden has emerged a syndrome, best known by the latter worker's name, of keratoconjunctivitis sicca with dryness of the mouth, nose, pharynx and larynx together with intermittent swelling of lacrimal and salivary glands and, in about two-thirds of cases, chronic rheumatoid arthritis. The syndrome is by no means rigid for individual cases often fail to show many of these symptoms. However, the pathological changes in the salivary glands are practically identical with those found in Mikulicz's disease. Occasionally evidence turns up, for example, in the form of poly-

arteritis nodosa of other organs, that suggests a manifestation of collagen disease apart from the rheumatoid arthritis. On the other hand, the lymphocytic infiltration and the not-infrequent occurrence of many plasma cells has recalled to some writers the early stages of Hashimoto's disease of the thyroid gland, and there is a further analogy in the severe fibrosis that sets in as the condition progresses. Time alone will provide the answer to these riddles; that there are entrancing puzzles cannot be denied.

Tumours of the salivary glands have been studied so extensively that the present contribution represents a mere micro-cosmos of the vast world of information that already has been collected. Nevertheless, it seems to represent a fair sample for it shows that the parotid gland is by far the commonest site of tumour growth, that most tumours are of the mixed and relatively innocent type, that they occur over a wide range of years and that they are somewhat more frequent in females than in males. Our experience agrees with that of the U.S. Armed Forces Institute of Pathology in referring the *mixed innocent tumours* most often to the tail or inferior part of the parotid, just beneath the ear lobule, in emphasizing their moist, greyish-white or blue semitranslucent surface, which is often mottled with cysts, haemorrhage and cartilage, their mixed epithelial and mesenchymal cellular structure with frequent transitions between epithelium and other types of tissue, and the tendency of about one in four to recur after surgical excision. We also agree that patients who show the *malignant* varieties are usually older than those in the benign class, that extensive necrosis is an ominous sign, that one or other malignant component may outgrow the area of origin so that the tumour may resemble adenocarcinoma, squamous cell carcinoma, giant cell tumours or spindle cell sarcoma with combinations of these, and that they spread to the cervical lymph nodes.

Our 9 *adenolymphomas* were removed from adult males, and each showed a pronounced lymphoid matrix grouped in close relation to acidophilic, papillary and cystic strands of epithelium. The epithelial cells were mostly arranged in two rows, the inner being tall columnar, the outer cuboidal or polygonal with vesicular nuclei and prominent nucleoli. However, arrangement was extremely variable and often without order. In only one instance could cilia be demonstrated, but mucus was not uncommonly stored within cells. We found no certain evidence of malignant change. Their origin remains a mystery; they have been thought to be teratoid, branchiogenic, derived from

thymic anlage or from parotid ducts included in lymph nodes.

Our examples of adenocarcinoma, whether cystic, acinar, spindle cell and myo-epithelial, or squamous cell, closely recall those described by other observers and differ in no striking way from such tumours growing in other localities. Our single case of oxyphil cell adenoma presented large, eosinophilic cells arranged in columns and cords only a few cells thick with a little fibrous stroma between. Lymphocytes were scanty in the interstices. It appeared to be benign.

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Treatment

My contribution is limited almost entirely to surgical treatment, and in particular to excision of salivary glands in whole or in part for tumours. Of the two major salivary glands, tumours are much more common in the parotid than in the submandibular. Sir Roy Cameron has already noted the curious infrequency of tumours of the submandibular gland. If one sees what appears clinically to be a typical primary tumour of the submandibular salivary gland, the chances are at least as great that it is something else, in particular some type of lymphoma involving the submandibular lymph nodes. Tumours similar to those of the major salivary glands may also arise in the numerous unnamed mucous salivary glands of the mouth and pharynx, and in the similar glands of the respiratory tract. The

commonest site for a tumour of these minor salivary glands is the posterolateral region of the hard palate. The principles of treatment of tumours of the salivary glands can therefore be epitomized by considering the treatment of tumours of the palate as representing the minor salivary glands, and of the parotid as representing the major salivary glands.

The essential surgical problem is similar in both sites. The commonest tumour, the mixed tumour, grows predominantly by expansion so that there is condensation and fibrosis of the surrounding normal tissues, and a plane of loose areolar tissue surrounding the tumour through which it can often be easily enucleated. But mixed tumours are not always completely encapsulated, loose tumour cells easily become implanted, and experience shows that, if enucleation is adopted as a routine, recurrence occurs too frequently for complacency. Thus, Ranger, Thackray and Lucas (1956) found 4 recurrences in 8 cases of mixed tumour of the palate treated by enucleation, the recurrences in some cases not developing until many years after the primary operation. In contrast, they found no recurrences in 10 cases of mixed tumour of the palate treated by wide excision. Moreover in both the palate and the parotid, tumours clinically indistinguishable from mixed tumours occur in which infiltrative growth is the rule rather than the exception. One of these tumours, the cylindroma or basilioma, constituted no less than 15% of all tumours of the palate in the series of Ranger *et al.* Wide excision at the primary operation offers the only hope of cure for patients with these infiltrating tumours. The few cases that I have had of tumours of the palate I have treated by diathermy excision of the tumours down to bone with a wide rim of the whole of the surrounding soft tissues. Subsequently I diathermy the bone. Bone necrosis is almost the rule, and the sequestrum may take months to separate. There may also be a fistula into the antrum but this usually closes. If the tumour encroaches on the alveolus, one or more of the corresponding upper molar teeth may have to be removed. The burden of treatment for the patient is thus considerable, but in return no patient has yet developed a recurrence, though I have been fortunate in not meeting any cylindromata.

In some sites such as the pharynx and parotid, the policy of wide excision irrespective of anatomical considerations may have to be modified because of possible severe functional disability. In the parotid, this difficulty is overcome by preliminary routine exposure of the facial nerve, and by the now well-established operation



FIG. 1.—Carotid arteriogram to show internal carotid artery bowed forwards over tumour.



FIG. 2.—Same case after removal of tumour to show internal carotid artery back in normal position.

of conservative parotidectomy, i.e. parotidectomy with conservation of the facial nerve. I do not propose to discuss in detail the operative technique of conservative parotidectomy, but will touch briefly on two points: the preliminary identification of the facial nerve, and the type of operation to perform.

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With regard to the type of conservative parotidectomy, some surgeons perform a total parotidectomy as a routine, the most notable advocate of this policy being Redon (1955). The arguments are partly pathological and partly technical. The pathological argument is that mixed tumours are usually multiple, and therefore that

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A conservative parotidectomy with complete preservation of the facial nerve may also be possible even though the tumour is infiltrating, providing that it is not infiltrating in the neighbourhood of the facial nerve. Sometimes, too, it is possible to preserve part of the facial nerve, and it is surprising how little facial paralysis may result even from cutting one of the two main subdivisions of the nerve provided that the plexiform connexions between the anterior terminal branches can be preserved.

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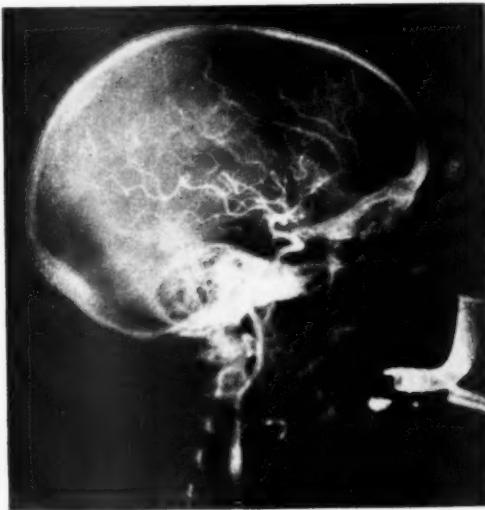


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Extensively infiltrating tumours and almost all tumours with facial paralysis will usually require total removal of the parotid with sacrifice of the facial nerve. Most but not all carcinomas will fall into this group. Contrary to common belief in the past, carcinoma of the parotid is rarely technically inoperable, since any superficially infiltrated structures such as the masseter and sternomastoid can be readily excised, and on the deep surface the plane of cleavage between the parotid and the styloid process, deep to which again lies the internal carotid sheath, is only obliterated in the very late stages of the disease. In spite of technical operability, the more acute and proliferative types of carcinoma are probably best not operated on but treated instead by radiotherapy. Again contrary to common belief in the past, radiotherapy may provide considerable palliation in this type of case.

Finally, I would like to draw attention to an operation which might be termed "mobilization of the parotid". I recently saw a patient with a tumour involving the IX, X, XI and XII cranial nerves close to the base of the skull. The tumour could only just be detected externally, but could be seen projecting into the nasopharynx and felt through the palate. A carotid arteriogram (Fig. 1) showed a marked bowing forward of the internal carotid artery over the tumour. An incision was made as for a parotidectomy and the trunk of the facial nerve with its lower main division identified. The parotid was then freed posteriorly from the external auditory meatus, mastoid, and sternomastoid, inferiorly from the posterior belly of the digastric, and deeply, after double ligation and division of the external carotid artery as it entered the parotid gland. The parotid could then be rotated forward round the axis of the facial nerve to give a good approach to the structures of the parotid bed. After resection of the posterior belly of the digastric and nibbling away of the styloid process up to its base, a good view of the tumour up to the base of the skull was obtained. The tumour was dissected off the internal carotid, and excised with the associated nerves up to the base of the skull (Fig. 2). Unfortunately the tumour was malignant and infiltrating through the foramina of the skull so that complete removal was impossible, but access up to this point was perfect. Though I have only performed the operation in this one case, I thought it was worth mentioning in this Section, Members of which are likely to see these

retro-nasopharyngeal tumours. The operation may also have a place in the approach to lesions of the upper end of the extracranial portion of the internal carotid.

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Mr. H. A. Kidd (London) said he had seen Dr. Diamant's clinic in Stockholm and had been most impressed with the enormous amount of research work which had been undertaken on the physiology of the parotid gland and the ingenious apparatus that Dr. Diamant had designed for such purposes.

Sir Roy Cameron classified the lymphoma as an innocent tumour but Mr. Kidd and several colleagues with whom he had discussed the matter considered that the lymphoma was frequently malignant as it recurred and metastasized. For recurrent attacks of subacute parotitis he had found that injection of Stenson's duct with 1 to 2 c.c. of streptomycin dissolved in hyalase would abort the attack. This might require to be repeated daily for three to four days. With regard to sialectasis, he had been using a method of treatment described by Dr. Diamant which consisted of ligating the duct from inside the mouth. This caused swelling of the gland in some cases and was followed by atrophy. It was a simple method which if it failed at least had done no harm and might obviate the performance of parotidectomy in severe cases.

He regarded all "mixed parotid" tumours as potentially malignant and therefore thought that the treatment should be by total parotidectomy with preservation of the facial nerve and did this in all cases. If only a partial parotidectomy was performed the tumour might be damaged and if there was a recurrence it was difficult to tell at an early stage whether the swelling was composed of tumour cells or reaction in the deep lying parotid which had been left behind. Also the operation for removal of a recurrence was more difficult as fibrosis occurred around the branches of the facial nerve. "Mixed parotid" tumour was a potential killer and recurrences were frequently malignant. They should therefore be treated early and radically.

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Section of Odontology

President—Professor F. C. WILKINSON, C.B.E., M.D., F.R.C.S., F.D.S.

Meeting
October 26, 1959

Professor F. C. WILKINSON delivered his Presidential Address entitled **Dental Education**.

Meeting
November 23, 1959

Dr. H. J. J. BLACKWOOD read a paper entitled **The Developmental Anatomy and Pathology of the Intra-articular Disc**.

Meeting
February 22, 1960

Studies on the Permeability of Tooth Roots to Penicillin

By I. CURSON, B.D.S., F.D.S., and F. L. JACKSON, M.B., M.R.C.S., L.R.C.P.
London

In the literature there are two main reports dealing with the permeability of the hard dental tissues to penicillin. Shuttleworth (1950) suggested that cementum was permeable, but his technique was criticized by Bennett and Miles (1955) who found, using an improved sealing method for both apical and coronal apertures, that none of the roots examined by them was permeable to penicillin. The latter results seem more in accord with the findings of Stones (1934) on permeability to dyes of molecular weight comparable to that of penicillin, and with those of Atkinson (1947).

The findings of Shuttleworth and of Bennett and Miles were in such direct conflict that it was decided to use a new technique for reinvestigation of the problem.

Methods

The method we have devised was designed to keep the sealed apical and coronal apertures out

of direct contact with the medium containing the test organism. Teeth were fixed vertically through a central hole in 3 in. diameter discs of 1/16 in. thick Perspex. Each disc was converted to a shallow dish by fixing cellulose tape around the edge. Melted nutrient agar, at 44°C, containing *Sarcina lutea* as test organism, was poured into the dish to a depth of 1/2 in. (Fig. 1). By means of this technique, any selected segment of a tooth could be so arranged as to be in contact with the medium. We have investigated particularly the coronal two-thirds of the root, since the known anatomy of the apical delta makes it almost certain that this root segment would permit the escape of penicillin from the root canal.

Freshly extracted single rooted teeth were placed in normal saline. The apical third of the root was sawn off under water, an opening was made into the pulp chamber through the crown, pulp tissue remnants were removed with a barbed broach and the canal was lightly reamed and irrigated with saline. It was planned to fix the tooth in the disc, seal the apical opening, and introduce penicillin solution on a paper point through the coronal aperture. The design required a very effective sealing agent for the apical aperture and the tooth-Perspex junction but, because of its isolated position under the disc, a less effective seal was permissible for the coronal opening.

Shuttleworth used as controls teeth completely coated with wax. It is clear that a negative result with a fully wax-coated tooth demonstrates that wax is not permeable to penicillin,

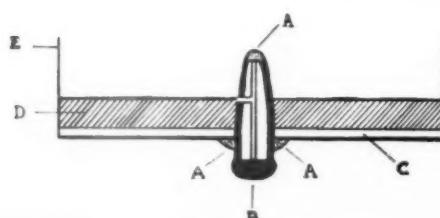


FIG. 1.—Diagram showing tooth mounting. A, Araldite seal. B, Wax seal. C, Perspex disc. D, Inoculated nutrient medium. E, Cellulose tape rim.

but does not test the effectiveness of the tooth-wax seal. The use of wax as a sealing agent of apical and coronal apertures was criticized by Bennett and Miles who considered that it would be likely to leak. Some preliminary experiments which we carried out using thick-walled capillary glass tubing instead of teeth showed that pink dental wax and sticky wax were unsatisfactory as sealing agents. It was therefore decided to use Araldite, an epoxy-resin, for the important sealing at the apex and at the tooth-Perspex junction.

It had become apparent in our preliminary experiments using 50 teeth that, if the teeth were allowed to dry at room temperature, some of them developed deep longitudinal cracks. In view of this, the teeth were selected after careful examination with a lens and in the technique used they were kept moist throughout.

The teeth were sealed, using only momentary and strictly localized drying by warm air of the areas where Araldite was to be applied. This left the coronal aperture still open and into this a cotton wick was wedged with a paper point. The other end of the thread trailed in water. The whole was kept in a Perspex box with a lid, so that the teeth were continually moist and in a humid atmosphere while the Araldite seal set. The wicks were then discarded and 1/25 ml penicillin solution, containing 8,000 units was soaked on to a paper point. This was introduced into the canal and the coronal aperture was sealed with wax. The medium containing the test organism was poured as described above, and the specimens were incubated in a humid atmosphere for eighteen hours at 32°C. They were then examined for zones of inhibition, and the form and size of any zone found was noted.

After the results had been recorded, the paper points were removed from the teeth, the specimen was inverted and a ring cut from 1 in. diameter rubber tubing was sealed with Vaseline on the Perspex around the crown. This formed a small cup and a solution of methyl violet was introduced into the canal by means of a syringe with a small excess in the cup to act as a reservoir, to test the tooth-Perspex seal. The approximate molecular weight of methyl violet is not markedly different from that of penicillin G. In no case was any leakage visible. The dye was introduced into the canal in order to test the apical seal and to demonstrate the possible route for the escape of penicillin, where this had occurred. The apical seals were always found to be satisfactory.

In order to facilitate the handling of several

teeth simultaneously, a large Perspex plate was prepared which would take twelve teeth, suitably spaced to avoid overlap of any zones of inhibition.

Results

In a pilot survey of 8 teeth using the method described we found that 6 gave zones of inhibition. The zones varied in diameter from a few millimetres to more than 4 cm, and there were also marked differences in their shapes. In some cases the zones were circular, the teeth being approximately central. Other zones were either flattened at one side or were reniform (Fig. 2). These findings suggested that penicillin

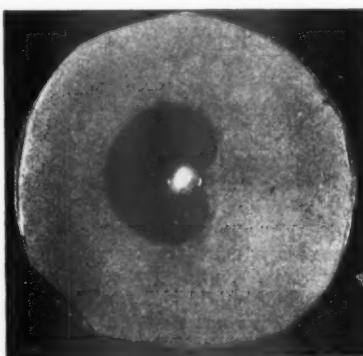


FIG. 2.—Showing eccentrically placed zone of inhibition.

could escape from some of the teeth, and that in some cases one aspect of the tooth was more permeable than another. It was therefore decided to examine 12 more teeth in detail to try to determine the possible routes for the escape of penicillin. Only 1 tooth showed no zone, although with 7 others the zones were very small.

The dye test, in addition to showing that the seals were intact, revealed some interesting appearances on the root surfaces. These may be roughly classified as (a) cementum faults, possibly due to extraction forceps, (b) a fine crazing of the cementum surface, (c) discrete spots related in position to the zone of maximum inhibition.

Faults of type (a) were associated with inhibition zones. The fine crazing of type (b) did not itself permit passage of penicillin or of dye, but it was made visible by the staining of the underlying dentine, and was possibly due to



FIG. 3.—Low power magnification of root surface showing crazed appearance and die spot, A, at the external aperture of a lateral root canal.

drying in the later stages of the experiment. The significance of the discrete spots of type (c) was revealed by sections, which confirmed our impression that they were the openings of lateral canals (Fig. 3).

Teeth which did not show zones were buried on the root and subsequent testing gave zones

related to the bur cut, a finding similar to that reported by Bennett and Miles.

Discussion

Our findings show that cementum which is intact is not permeable to penicillin, and in this we are in agreement with Bennett and Miles. It seems probable that some at least of Shuttleworth's results could have been due to the failure of the wax seal, with the penicillin escaping through a capillary space between the tooth and wax. It is clear, however, that some tooth roots may have faulty cementum, and the faults are not necessarily obvious when the tooth is fresh, moist and unstained. If a tooth has one or more lateral canals, penicillin can reach the surface of the root, and we have shown that this occurs in some cases. The demonstration of lateral root canals by the use of methyl violet is particularly simple and effective.

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Oral Tuberculous Ulceration

By H. P. COOK, M.B., M.D.S., F.D.S.
London

ULCERATION in the mouth from tuberculosis is a well-known phenomenon. It was formerly common when the chronic pulmonary disease could not be treated with the powerful chemotherapy available now. Therefore many open cases had as a complication ulceration of the larynx or the mouth. With the gradual disappearance of chronic pulmonary tuberculosis, ulceration of the mouth is becoming much more uncommon. The two cases presented show several features of interest, quite apart from their scarcity. Both are cases of mucosal ulceration.

Case 1

History.—Male aged 47, farm-worker. He complained of soreness and ulceration of the lower left gum and cheek for three weeks. A small fragment of tooth had been removed from the same area ten days previously and this had failed to heal. There were no relevant past illnesses.

On examination.—A ragged shallow ulcer affecting the left lower gingiva and buccal sulcus extended forwards from a partly healed socket in the molar region to the canine tooth. The adjacent sulcus was

most actively involved, and the ulcer there was covered by slough. This would fit into the description of "mouse eaten". The mucosa related to the first and second premolars had a raw inflamed look, sharply separated from the normal gum near-by (Fig. 1). Dental radiographs showed no abnormality.



FIG. 1 (Case 1).—Tuberculous ulceration of mucosa. Left buccal sulcus and lower alveolus.

but does not test the effectiveness of the tooth-wax seal. The use of wax as a sealing agent of apical and coronal apertures was criticized by Bennett and Miles who considered that it would be likely to leak. Some preliminary experiments which we carried out using thick-walled capillary glass tubing instead of teeth showed that pink dental wax and sticky wax were unsatisfactory as sealing agents. It was therefore decided to use Araldite, an epoxy-resin, for the important sealing at the apex and at the tooth-Perspex junction.

It had become apparent in our preliminary experiments using 50 teeth that, if the teeth were allowed to dry at room temperature, some of them developed deep longitudinal cracks. In view of this, the teeth were selected after careful examination with a lens and in the technique used they were kept moist throughout.

The teeth were sealed, using only momentary and strictly localized drying by warm air of the areas where Araldite was to be applied. This left the coronal aperture still open and into this a cotton wick was wedged with a paper point. The other end of the thread trailed in water. The whole was kept in a Perspex box with a lid, so that the teeth were continually moist and in a humid atmosphere while the Araldite seal set. The wicks were then discarded and 1/25 ml penicillin solution, containing 8,000 units was soaked on to a paper point. This was introduced into the canal and the coronal aperture was sealed with wax. The medium containing the test organism was poured as described above, and the specimens were incubated in a humid atmosphere for eighteen hours at 32°C. They were then examined for zones of inhibition, and the form and size of any zone found was noted.

After the results had been recorded, the paper points were removed from the teeth, the specimen was inverted and a ring cut from 1 in. diameter rubber tubing was sealed with Vaseline on the Perspex around the crown. This formed a small cup and a solution of methyl violet was introduced into the canal by means of a syringe with a small excess in the cup to act as a reservoir, to test the tooth-Perspex seal. The approximate molecular weight of methyl violet is not markedly different from that of penicillin G. In no case was any leakage visible. The dye was introduced into the canal in order to test the apical seal and to demonstrate the possible route for the escape of penicillin, where this had occurred. The apical seals were always found to be satisfactory.

In order to facilitate the handling of several

teeth simultaneously, a large Perspex plate was prepared which would take twelve teeth, suitably spaced to avoid overlap of any zones of inhibition.

Results

In a pilot survey of 8 teeth using the method described we found that 6 gave zones of inhibition. The zones varied in diameter from a few millimetres to more than 4 cm, and there were also marked differences in their shapes. In some cases the zones were circular, the teeth being approximately central. Other zones were either flattened at one side or were reniform (Fig. 2). These findings suggested that penicillin

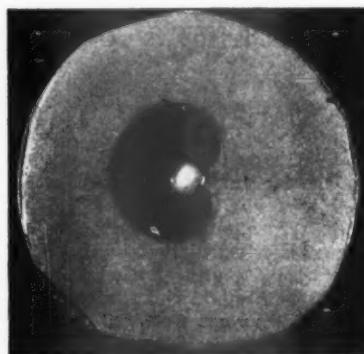


FIG. 2.—Showing eccentrically placed zone of inhibition.

could escape from some of the teeth, and that in some cases one aspect of the tooth was more permeable than another. It was therefore decided to examine 12 more teeth in detail to try to determine the possible routes for the escape of penicillin. Only 1 tooth showed no zone, although with 7 others the zones were very small.

The dye test, in addition to showing that the seals were intact, revealed some interesting appearances on the root surfaces. These may be roughly classified as (a) cementum faults, possibly due to extraction forceps, (b) a fine crazing of the cementum surface, (c) discrete spots related in position to the zone of maximum inhibition.

Faults of type (a) were associated with inhibition zones. The fine crazing of type (b) did not itself permit passage of penicillin or of dye, but it was made visible by the staining of the underlying dentine, and was possibly due to



FIG. 3.—Low power magnification of root surface showing crazed appearance and die spot, A, at the external aperture of a lateral root canal.

drying in the later stages of the experiment. The significance of the discrete spots of type (c) was revealed by sections, which confirmed our impression that they were the openings of lateral canals (Fig. 3).

Teeth which did not show zones were buried on the root and subsequent testing gave zones

related to the bur cut, a finding similar to that reported by Bennett and Miles.

Discussion

Our findings show that cementum which is intact is not permeable to penicillin, and in this we are in agreement with Bennett and Miles. It seems probable that some at least of Shuttleworth's results could have been due to the failure of the wax seal, with the penicillin escaping through a capillary space between the tooth and wax. It is clear, however, that some tooth roots may have faulty cementum, and the faults are not necessarily obvious when the tooth is fresh, moist and unstained. If a tooth has one or more lateral canals, penicillin can reach the surface of the root, and we have shown that this occurs in some cases. The demonstration of lateral root canals by the use of methyl violet is particularly simple and effective.

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Oral Tuberculous Ulceration

By H. P. COOK, M.B., M.D.S., F.D.S.

London

ULCERATION in the mouth from tuberculosis is a well-known phenomenon. It was formerly common when the chronic pulmonary disease could not be treated with the powerful chemotherapy available now. Therefore many open cases had as a complication ulceration of the larynx or the mouth. With the gradual disappearance of chronic pulmonary tuberculosis, ulceration of the mouth is becoming much more uncommon. The two cases presented show several features of interest, quite apart from their scarcity. Both are cases of mucosal ulceration.

Case I

History.—Male aged 47, farm-worker. He complained of soreness and ulceration of the lower left gum and cheek for three weeks. A small fragment of tooth had been removed from the same area ten days previously and this had failed to heal. There were no relevant past illnesses.

On examination.—A ragged shallow ulcer affecting the left lower gingivæ and buccal sulcus extended forwards from a partly healed socket in the molar region to the canine tooth. The adjacent sulcus was

most actively involved, and the ulcer there was covered by slough. This would fit into the description of "mouse eaten". The mucosa related to the first and second premolars had a raw inflamed look, sharply separated from the normal gum near-by (Fig. 1). Dental radiographs showed no abnormality.



FIG. 1 (Case I).—Tuberculous ulceration of mucosa. Left buccal sulcus and lower alveolus.

A biopsy was reported as showing "large numbers of multinucleated giant cells—characteristic of tuberculosis".

A chest radiograph revealed extensive tuberculous infiltration in both lungs.

On direct questioning he admitted to a productive cough of two years' duration with three to four mouthfuls of whitish sputum daily; also to exertional dyspnoea, but this was difficult to assess as he was doing a heavy manual job lifting grain sacks. There was no haemoptysis or chest pain. He thought he had lost some weight in the previous year as his clothes had become loose.

His wife had received sanatorium treatment for pulmonary tuberculosis seven years previously, but he had not been checked as a contact.

Case II

History.—Male aged 63, boat builder. One year previously he noticed an ulcer in the right upper premolar region. His dentist advised him not to wear his full upper denture, and on leaving this out the ulcer seemed to heal. Twelve weeks before he was seen another painless ulcer appeared, which involved the alveolus and labial sulcus in the upper incisor region. This was associated with occasional swelling of the upper lip. Finally a third separate painless ulcer appeared on the anterior part of the hard palate when he first came under my observation.

On examination.—This ulcer measured 0.5 cm across, had irregular but well-defined margins, and the floor was covered by yellowish slough. There was also a shallow irregular area of ulceration 3-4 cm in extent involving the anterior part of the upper alveolus and labial sulcus. A further irregular area in the upper left premolar region suggested a partly healed site of ulceration (Fig. 2). All these ulcers were painless.

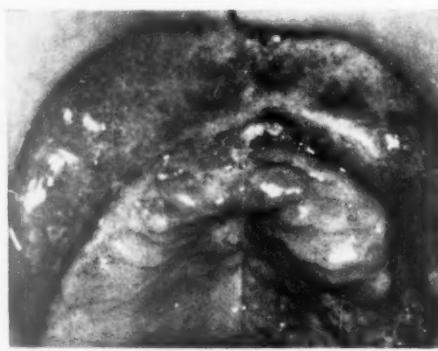


FIG. 2 (Case II).—Multiple tuberculous ulcers of mucosa. Left alveolus, anterior hard palate, and labial sulcus.

There were enlarged palpable nodes in the right upper cervical group. These were firm, discrete and mobile. There were no relevant illnesses and his Wassermann test was negative. Biopsies taken of

each ulcer all showed the same histology: "Ulceration of the epidermis. Connective tissue layer heavily infiltrated by granulation tissue showing tuberculid pattern. Giant cells numerous, some necrosis but no frank caseation—tuberculosis."

With Ziehl-Neelsen stain, acid-fast bacilli were seen in the tissue. Ordinary smears taken from the ulcers were also positive for acid-fast bacilli.

Chest X-ray showed tuberculous infiltration of left upper zone, with fibrosis and probable cavitation, also fibrosis in the right upper zone. Miliary spread throughout the lungs.

Careful questioning of the patient failed to produce any admission of feeling unwell. He admitted no weight loss, and the only chest symptom was slight pain associated with exertion or breathlessness. No choroidal tubercles could be seen.

To find this degree of widespread disease in an apparently fit patient was very surprising. Dr. B. Strickland has told me, however, in a personal communication that he has seen two or three similar cases of miliary tubercle in apparently fit old men.

Both these patients illustrate points of interest. Most standard textbooks hold that the classical tuberculous ulcer is a painful lesion. Neither of these patients complained of pain and this may have been due to the site of the lesions. The only painful tuberculous ulcer I have seen was on the tongue, and it seems reasonable to suppose that a lesion on a mobile organ would be more likely to give pain, than if it were at rest. The diagnosis should therefore not be ruled out on the absence of this one symptom.

The question of spread of the disease is also of interest in relation to these secondary ulcers. It is thought by most authors that ulceration occurs as a result of local infection by infected sputum, or by blood-stream spread. Probably each possibility is shown in these two patients. In Case I the ulcer was single, there was a history of local trauma and the sputum was positive. It was therefore probably the result of local inoculation. In Case II, blood-stream spread almost certainly was the cause, as the ulcers were multiple and there was typical miliary shadowing in the lungs.

It has, of course, been pointed out before that tuberculous ulcers may be discovered by the dental surgeon before pulmonary disease becomes evident. This is again exemplified by these two patients, and it is striking that both men walked into the surgery in such apparent good health that a firm diagnosis was not made until biopsy was performed.

I should like to thank Mr. R. Sutton Taylor for his permission to report these cases, and Dr. P. Hansell for the photographs.

Oral Surgical and Prosthetic Management of a Severe Hæmophiliac

By G. I. C. INGRAM, M.D., M.R.C.P., and DONALD WINSTOCK, M.B., F.D.S.
London

THE problem of oral surgery for hæmophiliacs has inspired many investigations and methods of treatment, both in the laboratory and clinically, over the past few years, and it is noteworthy that surgical progress has followed closely the advances made by the haematologists in their understanding of the blood disorder and its alleviation by replacement therapy.

Just over ten years ago, White and Mallett (1949) in America were advocating the extraction of one tooth at a time at fortnightly intervals in severe hæmophiliacs. Later Nichols and Baldridge (1954) reported a series of cases in which they employed several methods of managing dental extractions in hæmophiliacs, including elastic-band exfoliation, local haemostatics, ice-packs, suturing, splints, local pressure, anti-histamines and transfusions. Orr and Douglas (1957), in Glasgow, extracted up to 4 teeth at a time under local infiltration anaesthesia, using local measures and transfusions. Wishart *et al.* (1957) extracted up to 18 teeth at a time, transfusing blood or plasma. McIntyre *et al.* (1959), extracted up to 25 teeth at one session, emphasizing the necessity for prepared splints and transfusion of fresh blood without recourse to anti-hæmophilic globulin (AHG). In the same year, Nicholl and Findlay (1959), working in Belfast, reverted to earlier policies and stated that only one tooth at a time should be extracted in severe hæmophiliacs, maintaining that replacement therapy with plasma would not prevent bleeding from 10 or more sockets equally as well as from 1 socket. The one point on which all these authors seemed to agree, apart from the necessity for splints and transfusions, was an absolute contraindication of suturing of the soft tissues after extractions.

General Principles Governing Surgical Management

(1) An understanding of the haematological disorder is necessary. In hæmophilia, there is a deficiency, of a greater or lesser degree, of one of the blood clotting factors, known (tautologically) as anti-hæmophilic globulin, present in normal blood. The severity of the bleeding tendency is correlated with the degree of the deficiency which is thought to be constant for a given individual. Hæmophiliacs with less than 5% of the normal AHG activity are usually severely affected, bleeding spontaneously (from

serous and mucous surfaces, &c.), and after traumata continuing to bleed for abnormally long periods. Above 5% of normal, spontaneous bleeding is uncommon, but post-traumatic bleeding is unduly prolonged unless the AHG activity is at least 20-30% of average normal.

AHG enjoys only a short life in the plasma. If a hæmophiliac receives an infusion of AHG, the activity achieved in his blood falls at the rate of some 80% per day and in order to attain haemostatic levels, the material must be given rapidly. For instance, to prepare a severely affected subject for extractions, a litre of fresh human plasma must be infused in half to one hour before surgery. This will just suffice to raise the plasma activity to the critical level of 20-30% of normal, but within a few hours it will have fallen again. Thus, repetition of the infusion at intervals of twenty-four or even twelve hours is necessary to prevent post-operative bleeding, until healing is assured.

Concentrated AHG is available for transfusion, so providing the necessary activity in a smaller volume, and at a lower total protein concentration than for whole fresh plasma. Unfortunately, human AHG is prepared from fresh plasma, and so will always be scarce, and animal AHG, though very potent, is not yet free of species antigenicity, and should be reserved for life-saving measures such as urgent abdominal surgery or major injuries. Therefore plasma AHG, despite its drawbacks, is the usual choice for extractions.

(2) There will be periods in the day during which the AHG will fall to hæmophiliac levels, and disturbances to the wound in these periods will lead to bleeding. The wound must, therefore be protected from mechanical injury during the healing phase, e.g. by the use of dental splints.

(3) Despite the AHG deficiency impairing the clotting mechanism, the haemostatic functions of platelets and of the smaller vessels are apparently normal in hæmophilia. These components probably contribute to haemostasis by arresting the flow of blood from a wound so that, normally, a firm clot can form in the ends of the divided vessels, and this is thought to explain the immediate normal haemostasis in hæmophiliacs; but the bleeding may recommence in wounds after some hours if AHG is not given. Unfortunately, during the healing phase, the platelet and vascular components seem to lose their efficiency

for a time, so late post-operative bleeding will no longer respond merely to AHG but will require gentle pressure to the wound for at least five to ten minutes to arrest the bleeding while clotting occurs where it is needed, that is, in the ends of the bleeding vessels. Absorbable haemostatics are particularly useful here.

CASE REPORT

The patient, a white male, aged 39 and a known severe haemophiliac, presented in hospital complaining of a swelling over the left mandible and inability to open the mouth. The swelling first appeared three years previously, but subsided within three days after discharging intra-orally and the administration of a course of oral penicillin. The present swelling appeared five days prior to admission to hospital, and had increased in size gradually, with progressive numbness and paraesthesia of the left lower lip and jaw. Haemophilia had been diagnosed at the age of 6 and the patient remembered being cautioned by his doctor never, under any circumstances, to go to a dentist. His only previous dental treatment had been in 1952 when the upper central incisors were extracted, for which he was retained in hospital and given several transfusions of blood.



FIG. 1.—Photograph taken shortly after the first operation showing teeth as well as the facial swelling.

On examination.—A pale man with a large swelling over the left angle of the mandible, extending down into the anterior triangle of the neck and forwards to the premolar region. The swelling was fluctuant, adherent to the underlying bone and moderately tender to palpation (Fig. 1). The overlying skin was

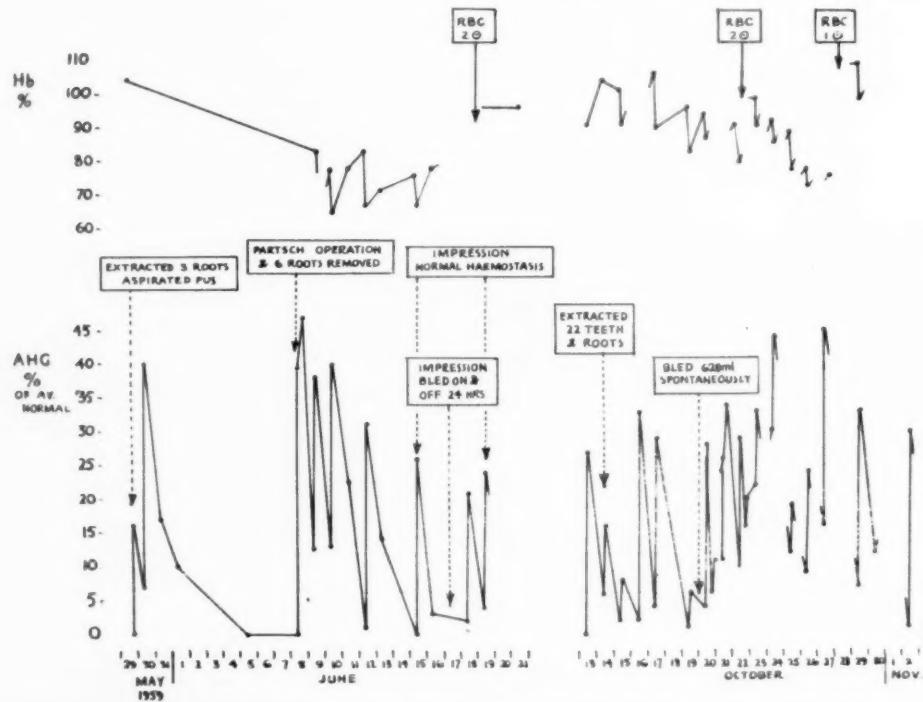


FIG. 2.—Haemoglobin concentrations, and plasma antihaemophilic globulin activity (AHG) recorded in the patient's blood. The saw-tooth haemoglobin curve is produced by the diluting effect of the rapid plasma infusions. The fluctuations in the AHG activity also follow the infusions. Breaks in the graph indicate that additional infusions were given at these times, but that tests were not made.

of a patchy, bluish discolouration, and this, together with the fact that the swelling was less tender than would have been expected for an acute inflammatory lesion, suggested that part, at least, of the swelling was attributable to haemorrhage. Because of the severe trismus inspection of the mouth was restricted to the carious teeth and retained roots anteriorly and a soft-tissue, turgid swelling occupying the left buccal sulcus.

Haemoglobin 104%. As an immediate measure of treatment, the patient's blood was grouped and human AHG equivalent to about 1 l. of fresh plasma was administered, together with one mega-unit of crystalline penicillin and 10 mg of Piriton, the latter drug to counteract any possible AHG or penicillin reactions.

Operation (29.9.59) was performed under endotracheal anaesthesia (Dr. C. A. Foster), which relieved the trismus sufficiently to permit a more detailed examination of the mouth. Several roots were present in the left mandible, those of the second premolar and first and second molars appearing to be intimately associated with the swelling, with pus discharging about these roots. This confirmed the X-ray appearances taken of this region which revealed an area of rarefaction suggesting a dental cyst. The involved roots were removed and the cyst cavity aspirated. Obliteration of the buccal sulcus by the swelling precluded the use of a conventional splint, so the root sockets were lightly packed with gelatin sponge and a stent splint was moulded to cover the lingual aspects of the sockets and to keep patent the aperture of the cyst; it was then extended outside the mouth, the portion of stent passing between the jaws being about 1 in. thick, thus acting as a prop to prevent a recurrence of the trismus post-operatively.

The immediate post-operative progress was uneventful and 900 ml of fresh plasma was administered the following day, together with the same doses of the aforementioned drugs. The AHG levels (Mrs. M. O. Matchett, F.I.M.L.T.) attained in the patient's plasma on this and following occasions are shown in Fig. 2, each peak corresponding to a transfusion. The short-term fluctuations in the haemoglobin readings indicate the degree of dilution of the patient's blood produced by the plasma transfusions, and the rapidity with which normal volumetric relationships were restored. By smoothing the haemoglobin graph an approximate idea of the overall blood loss may be obtained. A post-operative X-ray (Fig. 3) gave a clearer view of the cystic area in the left mandible. The stent splint was removed after four days; slight bleeding occurred on the sixth and seventh days, but responded well to local gelatin sponge therapy. Ten days post-operatively (8.6.59), a further operation was undertaken with anaesthesia as before. The upper left canine and first premolar and lower left canine, first premolar and third molar roots or teeth were removed. The cyst, which had perforated on the skin, was treated by the Partsch technique, part of the buccogingival lining being resected and the peripheral lining being sutured to the adjacent mucosa. The facial sinus was excised and the skin edges sutured to prevent fistula forma-

tion. The cyst cavity was packed with BIPP¹ incorporated in a gauze roll and a stent splint was moulded over the extraction sites. The transfusion was maintained with 800-1,200 ml doses of fresh plasma as indicated by the peaks on the chart of plasma activity. The BIPP pack was removed on the seventh post-operative day and an impression taken in stent, a temporary stent obturator being left in the cyst aperture. This impression proved to be inadequate and further impressions were taken on the ninth and eleventh post-operative days and an acrylic obturator subsequently inserted. It will be noted from Fig. 2 that the impressions taken first and last were covered by transusions, but not the second, and it was on this latter occasion only that abnormal bleeding ensued. A five-day course of oral penicillin was succeeded by a similar course of tetracycline. On the seventh post-operative day, the sutures were removed, intra- and extra-orally, uncomplicated by haemorrhage from the suture holes. The patient was discharged from hospital twelve days after the second operation. Two weeks after discharge, the use of the obturator was discontinued since the lateral walls of the cyst cavity had contracted sufficiently to render the cavity self-cleansing, i.e. no undercuts to encourage food retention. Histology of the resected lining (Dr. M. S. R. Hutt) showed fibrous and granulation tissue lined by squamous epithelium.

The patient was readmitted four months later for a total clearance of the remaining teeth and roots, 22 in all (14.10.59). Full dentures were constructed on models trimmed as for a clearance, alveolectomy and insertion of immediate dentures. Operation was performed under similar conditions of anaesthesia and antibiotic cover as previously. All the teeth and roots were removed, the gum flaps reflected and the alveoli trimmed with chisels and bone nibblers, except in



FIG. 3.—X-ray after the Partsch operation.

those regions where the sockets were shallow. The extent of the alveolectomy was such that the gum flaps could be coapted without undue tension. Redundant gingival tissue was resected and the resultant flaps sutured with interrupted silk sutures after the sockets had been lightly packed with gelatin

sponge. The dentures were inserted and adjusted where necessary. A crepe bandage was applied from chin to vertex to maintain the mouth closed until consciousness was regained.

The antihaemophilic treatment during the post-operative period may be deduced from Fig. 2. Some of the transfusions were of fresh plasma and some of concentrated human AHG, for which we are indebted to Dr. W. D'A. Maycock of the Blood Products Laboratory of the Lister Institute. Since after the Partsch operation the plasma AHG levels following transfusions had generally tended to fall (see Fig. 2, June 9 20), it was feared that an anti-AHG was beginning to develop in the patient's blood, provoked by the transfusions; and, therefore, on this occasion, transfusion was less vigorous than in the initial post-operative period. This was a mistake, because serious bleeding occurred on October 20, when some 600 ml of blood were lost over five hours, despite local measures, ceasing only when fresh plasma also was given. Thereafter, transfusion was more intensive, usually being given twice daily. The minimum AHG activities (i.e. just before transfusions) were on the whole higher than on the regimen of one transfusion daily, and thereafter any further bleeding was controlled by local measures. By the seventeenth post-operative day all bleeding had ceased and on the eighteenth day the dentures were relined; the patient was discharged two days later, i.e. three weeks post-operatively. When seen eight months after the first admission to hospital, the gums were well healed and an X-ray of the left mandible showed obliteration of the cyst cavity (Fig. 4).



FIG. 4.—X-ray taken eight months post-operatively showing obliteration of cyst cavity.

Discussion

The treatment carried out for this patient, both as regards his acutely infected dental cyst and a clearance with alveolectomy and the insertion of immediate dentures, closely follows the lines of treatment which might be adopted for a non-haemophiliac. Several points emerge from this experience. (1) Contrary to most firmly held concepts, suturing of both skin and mucosa may be adopted in haemophiliacs,

provided that an adequate AHG blood level is maintained. Indeed, suturing the gum flaps allows one to insert a splint with less fear of vertical displacement of the gum margins. It is stressed that at no time during the post-operative periods did submucosal haemorrhages occur—the hall-marks of soft-tissue bleeding consequent upon sutured gum flaps. We have carried out this suturing regimen in less severe haemophiliacs and in cases of Christmas disease and have found that in these cases, suturing can obviate the need for splints, since coapted gum flaps are almost self-protecting, provided that soft food is taken during the early healing phases. Tight suturing is not advocated, since bleeding, if it does occur, is best drained into the mouth rather than into the submucous tissues.

(2) Stent splints, unlike acrylic, can be moulded at the time of operation, can be modified later by simple heating and survive long enough without significant distortion at mouth temperature to carry the patient over the post-operative danger period.

(3) Where a clearance is contemplated (and this is the method of choice in haemophiliacs with mouths full of carious, broken-down teeth), it seems quite feasible to make splints in the form of full dentures. Such dentures subserve three functions, viz. (a) Protection for the immediate post-operative period. (b) Pressure, which may be applied when and where indicated for the arrest of localized areas of oozing by the addition of stent to the acrylic flanges to help retain gelatin sponge in the sockets. (c) Permanent prostheses, when relined at suitable intervals after the bleeding phase has passed.

Enough is now known about the replacement of AHG by transfusion to put the acute management of haemophiliacs on a par with the treatment of diabetics with insulin and AHG can now offer so effective a cover for surgery that the procedures do not have to be modified excessively because of the basic hemorrhagic disease.

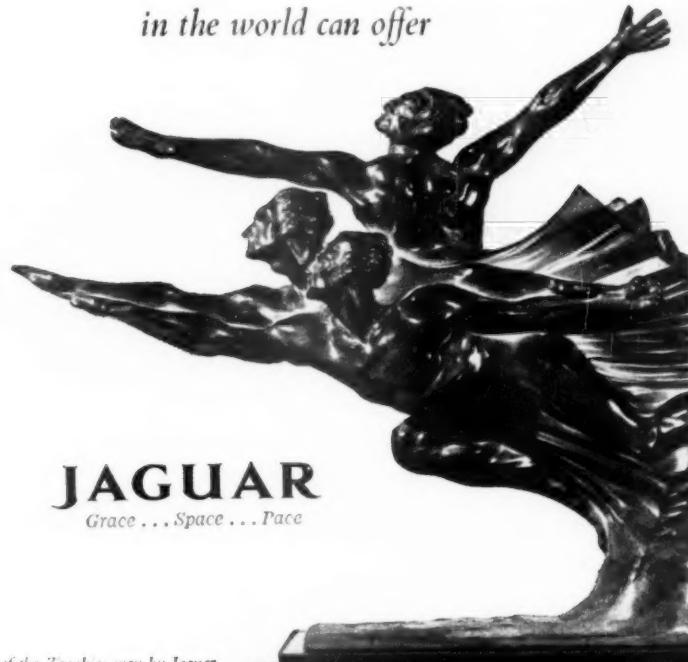
We wish to thank the Photographic and Radiology Departments of St. Thomas' Hospital for the illustrations.

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BOOK REVIEWS

Textbook of Toxicology. By Kenneth P. DuBois, M.Sc., Ph.D., and E. M. K. Geiling, Ph.D., M.D. (Pp. x + 302; 2 illustrations. 52s.) New York: Oxford University Press. 1959.

After a short interesting historical introduction there is a useful chapter on the general principles of toxicology. The general standards for toxicity for the more important industrial poisons are those of the American Industrial Hygiene Association. The medico-legal aspects are all related to U.S. law and this for Britain makes it a matter more of academic than practical interest. However, the procedures recommended for post-mortem work and the preparation of specimens for later examination are very practical. The rest of the book summarizes in moderate detail the effects of those substances whose toxic actions may threaten modern man in medicine, industry and not least in the home. The lessons and warnings are valid on both sides of the Atlantic. The unfortunate sequelæ of the available tranquillizers and soporifics justify the concern expressed in this country. Practically all the literature referred to is in English but the coverage on the whole is adequate. While there are points where the individual reader may disagree with the authors, the subject matter is up to date and will serve as a useful introduction to further reading. After all, the book is a teaching course of toxicology and since the present difficulty is where exactly toxicology should be taught a text which at least outlines the length and breadth of the subject must of necessity have its sphere of usefulness.

Toxic Aliphatic Fluorine Compounds. By F. L. M. Pattison, M.A., Ph.D., F.R.I.C., F.C.I.C. (Pp. xi + 227; illustrated. 18s.) Amsterdam, etc.: Elsevier Publishing Company. 1959.

These compounds form a remarkably interesting series of substances whose main toxic effects depend primarily on the possibility of and the degree of formation of fluoroacetic acid as the result of their β -oxidation within the organism. Interest in these types really started with the unravelling of the toxic effects of gifblaar, a South African stock poison which was finally shown to be due to potassium fluoroacetate. The intense toxicity of these types of substances made them potential chemical warfare agents which, however, were never used and they are now the source of powerful pesticides and at least one powerful general anaesthetic. Most of the results reported have been obtained in mice. There have fortunately been but few cases of poisoning, and those accidental, in man. However, sufficient is known of the general mechanism of action to allow a reasonable forecast from animal results. Using mouse toxicity as an index the series show a

surprising degree of orderliness in their symptoms as a result of their blocking the action of aconitase, one of the enzymes of the tricarboxylic acid cycle. Some of these substances have actually been used to work out certain phases of the cycle. The author's seventeen years' interest in this field has resulted in an interesting, readable and well-balanced study of the chemistry, biochemistry and pharmacology of compounds of this nature and should stimulate further interest and may yield results of as great or greater importance than those already described.

British Pharmaceutical Codex 1959. (Pp. xxix + 1301. 70s.) London: The Pharmaceutical Press. 1959.

In virtue of its status and its usefulness this is still an essential. It reflects the more conservative position in therapeutics discarding these remedies which have finally been found wanting. The introduction as usual summarizes the changes since the last edition and its addendum—the general policy underlying the selection of preparations for inclusion has remained unchanged. The number of deletions is smaller than in earlier editions—perhaps an indication of the generally increased efficiency of the drugs now in use. The relation of drugs to the Therapeutic Substances Act occasionally leads to difficulties, more especially with the newer preparations, and comment is made on the difficulties experienced in relation to the monograph on poliomyelitis vaccine. The difficulties involved during the stabilization period of a new drug when it is still in the hands of the original manufacturer are mentioned and the decision to wait until the drug has, as it were, settled down both in usage and composition is a wise one for a book of standards. There are three new appendices of which the table of milliequivalents may be considered in many ways complementary to the older table of isotonic solutions. Comments on the codex by reviewers are difficult since it is continually being commented on in the intervals between issues by its various committees.

Biochemistry of Blood in Health and Disease. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. (American Lecture Series No. 384. Pp. ix + 543; illustrated. £6 6s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This excellent compendium of biochemical knowledge of blood covers exhaustively the chemical changes in plasma and cells from both the physiological and pathological aspects. The avowed aim of the author is "to present the

newer knowledge of human blood in health and disease in the light of chemical research, clinical experience and medical necessity". With certain reservations, these objectives are attained. For instance, it is probably inevitable, but regrettable, that in a book of this size, which must take several years to assemble, there are so few references to work since 1955. In some fields this does not matter, but in others where advances are taking place so rapidly, such as in the haemoglobopathies, coagulation and serum enzymes, some of the recent major advances receive no mention.

Blood is considered under three physiological functions: transport, regulation and defences. The chapter on electrolytes, acid-base balance and gas exchanges are clear and detailed and the clinical changes are well discussed. Much of the work on blood enzymes is historical and the recent advances in bilirubin metabolism are not included. The chapters on red cell chemistry are extremely detailed but difficult to read because of the compression of facts and references. Coagulation of the blood is clearly recounted, but detailed consideration of the knowledge that has accrued from the use of the thromboplastin generation test has been omitted.

In spite of these recent omissions this book should prove an excellent reference work for there are few inaccuracies and references are abundant and useful. Most of it is clearly written and there are many useful figures and plans which help the unfamiliar reader to follow the complexities of modern chemistry. There is a useful appendix of normal data and a detailed and accurate index. The book will be of value to the clinician and biochemist who are not specialists in a particular subject, and even to those who are it is sufficiently comprehensive to fill in the gaps in their knowledge of their field.

Medical Helminthology. By J. M. Watson, D.Sc., A.R.C.S. (Pp. xi + 487; illustrated. 84s.) London: Baillière, Tindall and Cox. 1960.

This book is designed to bring within short compass the most important and recent information concerning the helminth parasites of man, and to stimulate research by indicating some of the questions awaiting solution. It is based on lectures given to medical students in the American University of Beirut.

The general introduction includes the principles of helminth infections; a systematic account of the parasites follows; and the clinical and public-health aspects of infection, their diagnosis, treatment and prevention are discussed. The book was begun in 1952 and since then very many advances—some of the greatest practical im-

portance—have been made, and these are incorporated in a valuable appendix.

It is becoming impossible for one author to produce a book on such a rapidly expanding subject as medical helminthology, but as far as this is possible, Dr. Watson has succeeded. In attempting such a task a writer reflects his own attitude to the subject, which, in this case, is unusually refreshing.

The book is perhaps a little lengthy for the undergraduate, and for the immediate post-graduate student in tropical medicine, but gives to the young research worker a comprehensive and stimulating introduction to the subject.

The Physiological Basis of Diuretic Therapy. By Robert F. Pitts, Ph.D., M.D. (Pp. xiv + 332; illustrated. 78s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

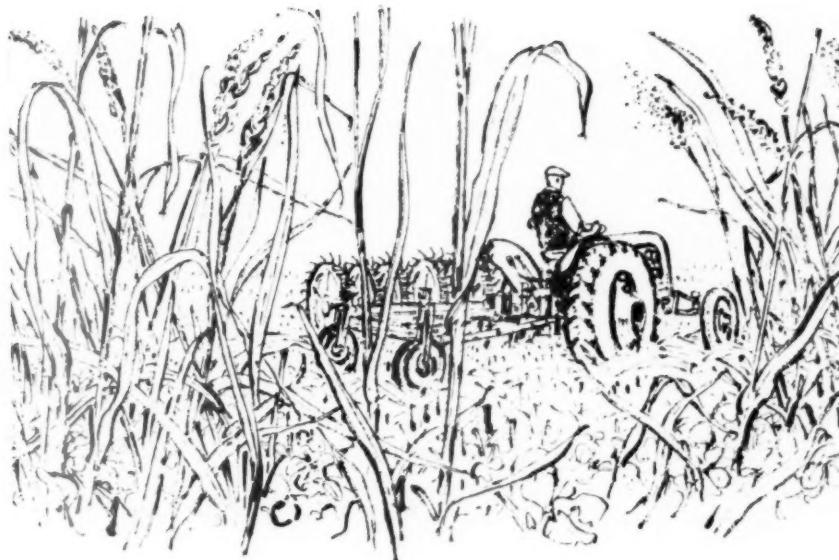
One of the most satisfying results of physiological research on the kidney, as far as the clinician is concerned, is the influence this has had in the treatment of oedema by diuretic therapy. Really spectacular advances in diuretic therapy have developed, especially during the past ten years, which have helped to advance the subject beyond the point reached by the discovery of the diuretic effect of the organomercurials some forty years ago.

Dr. Pitts, Professor of Physiology at Cornell University, has been prominent among those who, during the past decade or so, have carried out those critical experiments which have done so much to explain kidney function and ways of influencing it. Dr. Pitts' book is indeed a masterly review of this physiological work.

Dr. Pitts' account of his subject begins with a discussion of fundamental principles concerned with the distribution of water and electrolytes in the body, the chemical composition of the body fluids and their regulation, the role of the kidney in water and electrolyte homeostasis, and mechanisms of oedema. The first six chapters are devoted to this basic physiology.

Part II describes the physiological basis of the use of practically all known diuretics which are worth discussing. It is perhaps an interesting reflection of the speed with which this subject has changed at the present time that Dr. Pitts' book, although published in 1959, gives what must now be regarded as rather inadequate treatment of the chlorothiazide type of diuretic and the clinical usefulness of the steroid spiro lactones.

As is to be expected from Dr. Pitts, the whole book is written in a masterly and authoritative fashion. It can be read with profit by anyone interested in the treatment of oedema and it can be thoroughly recommended.



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